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SERUM "PROSTATIC" ACID PHOSPHATASE AND CANCER OF THE PROSTATE*

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THE acid phosphatase content of malignant prostatic tissue is regarded as an example of the retention by the neoplastic growth of a biochemical characteristic of the fully differentiated tissue of origin. For fifteen years the serum acid phosphatase determination has been accepted as an adjuvant method for the diagnosis of cancer of the prostate. The findings of elevated values have been correlated with advanced cancer of the prostate with spread to bones and rarely with nonmetastatic disease. As a consequence, the finding of an elevated serum acid phosphatase in a patient with clinical evidence of localized cancer of the prostate whether or not accompanied by x-ray evidence has signified metastases, and the management of such patients has been solely palliative.

A study of our experience and that of others reveals that even in metastatic cancer of the prostate, a positive correlation with serum acid phosphatase occurs in only about 50 per cent of these cases. Clearly, there is a need for improving this situation and for searching for the explanation of normal values in nonmetastatic cancer of the prostate. Advances in this area might conceivably bring the patient with cancer of the prostate to the attention of his physician at earlier and perhaps curable stages of his disease.

A clue to a possible biochemical approach to this clinical problem was forthcoming from the observation that L-tartrate was a potent inhibitor of acid phosphatase present in crude extracts of human prostate as well as of liver, spleen and kidney. Three circumstances are necessary for the practical application of this information: that the prostate gland be the major source of tartrate-sensitive serum acid phosphatase; that the amount of this element in the serum be sufficient for its measurement; and that an accurate sensitive method be developed for this purpose.

Regarding these prerequisites it is known that the human prostate gland is by far the richest tissue source of acid phosphatase. Moreover, a method for estimating the tartrate-sensitive component of the serum acid phosphatases was developed in 1953.[1] At that time values above 0.5 King–Armstrong units of tartrate-inhibited acid phosphatase were rarely encountered whereas abnormal values were found in cancer of the prostate even though the results of the conventional King–Armstrong procedure were often within normal limits. A second report[2] pointed to the diagnostic potentialities of the new procedure and indicated that the measurement of tartrate-sensitive serum acid phosphatase gave a more accurate index of the "activity" of prostatic cancer. The relative ease with which the prostate gland can enrich the circulation with tartrate-sensitive acid phosphatase was demonstrated by massage of the prostate gland in a number of patients. Such effects were not seen after massage in prostatectomized subjects.[3] Since an elevation of tartrate-sensitive acid phosphatase has so far been associated only with disorders of the prostate — in particular, with cancer of the prostate — the term "prostatic" has been introduced to provide a probable tissue identification of this moiety of the serum acid phosphatases.

In the interim, reports have appeared that confirm the original findings and the validity of the principle of partitioning serum acid phosphatase into tartrate-sensitive and insensitive fractions.[4-10]

The purpose of the present paper is to report our experience with 91 cases of cancer of the prostate and with 1198 patients who had other diseases, thereby completing the documentation of the initial findings. The evaluation of these data has afforded information concerning the clinical value of serum "prostatic" acid phosphatase and has added to our understanding of the relation of this blood component to cancer of the prostate.

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Material and Methods

Clinical Material

Studies were done on patients from a variety of sources. Patients of the Holy Ghost Hospital were chronically ill and were confined to bed, as a rule. Those from the New England Center Hospital were mainly patients admitted for diagnosis whereas the patients of the Boston Dispensary were ambulatory outpatients. Material from two urology outpatient clinics, one at the Peter Bent Brigham Hospital and one at the Boston Dispensary, was studied. Blood specimens were collected from patients with miscellaneous disorders from the Boston City Hospital and other hospitals. Total and "prostatic" acid phosphatase was determined in duplicate on each serum by the method of Fishman and Lerner.[1]

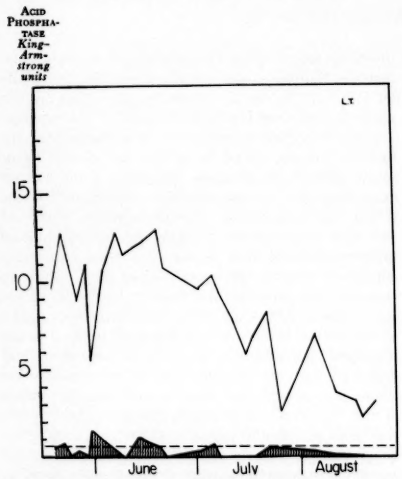

FIGURE 1. *Presence of a High Total and Normal "Prostatic" Serum Acid Phosphatase in a Woman with Cancer of the Breast under Meticorten Therapy.*

Results

Clinical Specificity of Abnormal "Prostatic" Acid Phosphatase Levels

A large number of serums were analyzed for serum total and "prostatic" acid phosphatase by the method of Fishman and Lerner to assess the clinical specificity of abnormal values.

In male subjects "prostatic" acid phosphatase is elevated regularly above 0.6 King–Armstrong units only in cancer of the prostate (75 of 91 patients). In other types of cancer 7 out of 121, and, in the noncancer group, 30 out of 786, exhibited abnormal values. Fifteen of these 30 occurred in benign prostatic hypertrophy. In many cases (16 out of 30) only a single determination was possible because these patients were not available for follow-up studies; in the remaining 14, the second serum gave a "normal" result. It is possible that rectal examination before the withdrawal of blood from a number of these subjects accounted for the first "abnormal" values,[3] although the possibility of an unsuspected cancer of the prostate has not been excluded.

In the 173 female subjects no correlation with any pathologic state was evident so far as abnormal "prostatic" values were concerned. Four of the 10 abnormal figures were found at the dividing line (0.60 units) as pointed out below. It is not surprising that serum from female subjects may on occasion contain some "prostatic" serum acid phosphatase in view of the findings[11] that organs other than the prostate may be the site of tartrate-sensitive phosphatase.

In cancer of the breast 2 subjects with abnormal total acid phosphatase were discovered: patient L.C. — total, 7.5, and "prostatic," 0.1, King–Armstrong units[1] — and patient L. T. — total, 10.0, and "prostatic," 0.45, King–Armstrong units (Fig. 1). The elevated serum acid phosphatase in such cases is not due to an increase in the L-tartrate-sensitive component.

Abnormal Prostatic Acid Phosphatase in Male Subjects with and without Cancer of the Prostate

These patients are classified in Table 1 in the following groups:

TABLE 1. *Abnormal Serum ("Prostatic") Acid Phosphatase in Cancer of the Prostate.*

Group	Acid Phosphatase	Cancer of Prostate		
		Proved Cases*	Probable Cases†	Questionable Cases‡
1	Normal total; normal "prostatic."	15	2	1
2	Normal total; abnormal "prostatic."	48	4	13
3	Abnormal total; abnormal "prostatic."	28	1	2
2 & 3	Abnormal "prostatic"	76	5	15

*91 cases.
† 7 cases.
‡16 cases.

Cancer of the prostate

Proved. In the majority of cases (72 out of 91) the diagnosis was based on positive histologic findings either on biopsy or on autopsy material. In the others a combination of findings — namely, that of a stony-hard, nodular prostate and x-ray evidence of osteoblastic metastases — constituted proof of cancer of the prostate.

Probable. These cases were characterized by a positive cytologic finding of cancer in the prostatic

smear together with a gland regarded as suspicious of prostatic cancer by the urologist.

Normal. These comprised cases in which the most careful clinical examination could not reveal any suggestion of prostatic cancer. Among these 1190 patients there were 48 in whom an abnormal serum "prostatic" acid phosphatase was observed. It is contended that all these cases with elevated serum prostatic acid phosphatase values in the absence of tangible clinical evidence should not be classified as "false-positive" reactions. It is well known that the most thorough urologic examination detects only a fraction of the cancers of the prostate that may actually be present. Accordingly, it is necessary to segregate and follow these patients

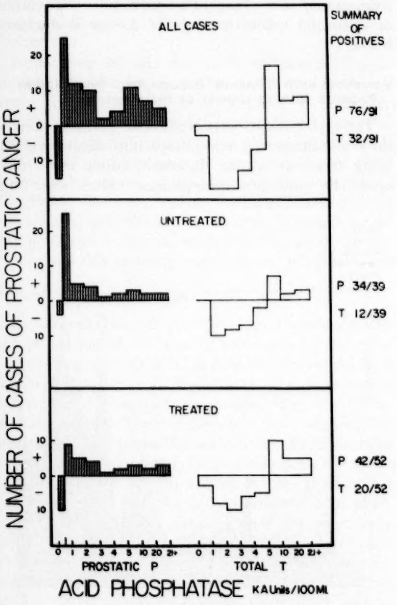

FIGURE 2. *Occurrence of Elevated Serum Acid Phosphatase Levels in Cancer of the Prostate. "Prostatic" data are shaded.*

with special care so that cancer of the prostate may be found or its absence definitely established at a future date. In 15 of these subjects such abnormal values were above 1 unit of "prostatic" serum acid phosphatase, and these values are therefore considered "abnormal." In 33, the serum acid phosphatase was on a single occasion found to be 0.6 to 1 unit. Even though in 15 of these cases normal values were obtained on other occasions, we have classified them separately and labeled them as borderline.

The 91 cases of proved cancer of the prostate were correlated with elevated total and "prostatic" serum acid phosphatase (Fig. 2).

Of significance in this category are the statistics indicating the degree of clinical accuracy of the Fishman–Lerner procedure and the results that are germane to the nature of the pathologic process itself.

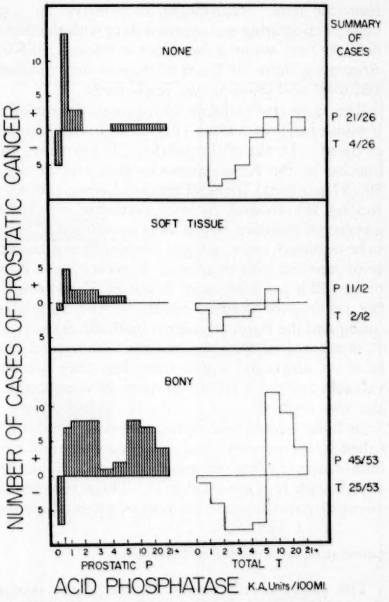

FIGURE 3. *Serum Acid Phosphatase Correlated with the Presence and Type of Metastasis from Cancer of the Prostate. "Prostatic" data are shaded.*

Performance of the Fishman–Lerner Technic

The basis of this study has been the comparison, in the same patient, of results obtained by the King–Armstrong (total acid phosphatase) and the Fishman–Lerner ("prostatic" acid phosphatase) methods. The selection of the critical level that is taken to separate positive from negative findings in these two methods is somewhat arbitrary. The value of 0.5 King–Armstrong units of "prostatic" acid phosphatase was taken earlier as a tentative limit of normal on the basis of a distribution curve.[2] This figure was also accepted by Bodansky,[12] who arrived at a value of 0.53 by adding 3 standard deviations (0.12) to his mean value (0.17) in 33 blood-bank donors.

From an analysis of the present data the mean "prostatic" acid phosphatase and its standard deviation for 1175 subjects is 0.15 ± 0.2 units. Therefore, a value of 0.6 King–Armstrong units for "prostatic" acid phosphatase is now preferred since it represents the mean plus somewhat more than 2 standard deviations and because it is based on an evaluation of many more patients than before.

For the total acid phosphatase (1.8 ± 0.8) the dividing line of 4.0 or 5.0 King–Armstrong units makes little difference in the conclusions to be drawn from the data. Accordingly, to preserve the possibility of comparing our previous data with the present ones, we have adopted the values of 0.6 and 5.0 King–Armstrong units for limits of normal for "prostatic" and total acid phosphatase, respectively.

The untreated patients with proved cancer of the prostate fared as follows (Fig. 2, right-hand column of data): 12 out of 39 patients (31 per cent) were positive by the King–Armstrong test, and 34 out of 39 (87 per cent) by the Fishman–Lerner procedure. Among the treated patients (estrogen), a greater number of negative results were encountered, as was to be expected, since estrogen frequently depresses the serum enzyme level to normal. However, some 20 out of 52 (38.5 per cent) and 42 out of 52 patients (81 per cent) gave positive results by the King–Armstrong and the Fishman–Lerner methods, respectively. It is recognized that the statistics on treated cases have no diagnostic significance, but they are both valuable and valid for the purposes of comparison of the two methods.

In both treated and untreated cases, attention is called to the numbers that exhibited abnormal prostatic values in the presence of normal total acid phosphatase findings (Table 1). These represent 48 out of 91 patients, or 53 per cent of the total number.

Correlation with Spread of Disease

The patients with proved cancer of the prostate were divided into categories of bony metastases (with or without soft-tissue spread), soft-tissue metastases and no metastases. It is evident from Figure 3 that in subjects with cancer of the prostate without metastases the serum prostatic acid phosphatase was abnormal in 21 of 26 cases whereas the total acid phosphatase was abnormal in only 4 of 26 cases. In patients with soft-tissue metastases, the serum prostatic fraction was abnormal in 11 of 12 cases whereas the total acid phosphatase was abnormal in only 2 out of 12. When bony metastases were present there was some improvement in the accuracy of the conventional acid phosphatase procedure, but the "prostatic" acid phosphatase was abnormal in almost twice as many cases.

It is justifiable to conclude, therefore, that the Fishman–Lerner method gives abnormal results in cancer of the prostate more frequently and at an earlier stage of the disease than the King–Armstrong procedure.

One important question concerns the time in the development of prostatic cancer at which one might expect to detect abnormal "prostatic" acid phosphatase in the blood serum (this subject is also considered below in the discussion of figures on long-term studies). The information available on patients without proved metastases shows that 8 had stony-hard, large prostates, 3 exhibited a single hard nodule, and 1 possessed a clinically benign gland. Another,[14] whose case history lacked a description of the prostate, exhibited a microscopic adenocarcinoma of the prostate at autopsy. The serum prostatic acid phosphatase showed abnormality on 3 occasions out of 8 determinations in the three-week period before death from cancer of the lung. The question of the relation of abnormal values to stage of disease is discussed below.

Variation with Time of Serum Acid Phosphatase in Patients without Cancer of the Prostate

Ten such patients were studied for periods of one to three months, serum acid phosphatase determinations being done at regular intervals, often three days apart. Prostatic acid phosphatase values were uniform and within normal limits. This study provides some information regarding the variation of levels in the blood of total and prostatic acid phosphatase as a function of time and serves as a basis of reference for evaluation of the long-term studies with and without hormone administration.

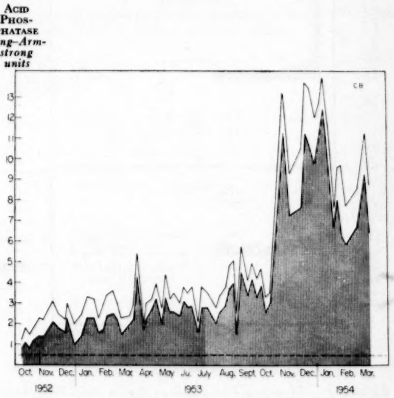
Acid Phosphatase King–Armstrong units
C.B.
Oct. Nov. Dec. Jan. Feb. Mar. Apr. May Jun. July Aug. Sept. Oct. Nov. Dec. Jan. Feb. Mar.
1952
1953
1954

FIGURE 4. *Long-Term Study of a Patient Admitted to the Hospital with Localized Cancer of the Prostate. Metastatic x-ray series were performed on four different occasions, the latest being in February, 1954. All were negative for bony lesions. "Prostatic" data are shaded.*

Correlations with Hormone Therapy

Cessation of Estrogen Treatment

An appreciable number of patients with cancer of the prostate exhibiting normal values for prostatic acid phosphatase do in time show a rise in the prostatic component of the serum acid phosphatase that may or may not be great enough to allow the total acid phosphatase to reach abnormal values. These findings provide some indication of the degree of suppression obtained with estrogen as evidenced by the time required for the prostatic component to become abnormal after cessation of hormone administration. It is important to note that in one long-term study without estrogen (Fig. 4), the serum prostatic acid phosphatase was consistently elevated for more than a year before the total acid phosphatase became uniformly abnormal. In other cases the interval was shorter.

In the cases that did show a rise in "prostatic" acid phosphatase, this usually became evident three to six weeks after cessation of estrogen therapy. A smaller number of patients seemed to have reached a stage of endogenous tumor control since no change in serum "prostatic" acid phosphatase or worsening of their disease followed the omission of exogenous estrogens. Therefore, in many cases, the maintenance of a normal acid phosphatase value after the cessation of estrogen was a sign of endogenous control of the tumor, and this fact suggested a better prognosis.

Administration of Estrogen

In accordance with our previous experience, the administration of estrogen to patients with prostatic cancer who have elevated values usually results in a fall in the serum acid phosphatase that is due to a decrease in the prostatic component (Fig. 5). Occasionally, normal levels of prostatic acid phosphatase are reached and persist for some time. These findings fit well the earlier observations of others on the effect of stilbestrol therapy in cancer of the prostate. It should be noted that the fall in prostatic acid phosphatase with estrogen therapy does not necessarily mean that the patient becomes clinically improved. This is particularly true if the value fails to reach normal. Also, there have been several patients whose prostatic acid phosphatase values were suppressed by estrogen therapy to normal levels but who nevertheless died of widespread disease while their phosphatase remained low.

Administration of Androgen

Previously, it was observed that the daily administration of 100 mg. of testosterone failed to raise the serum "prostatic" acid phosphatase in patients without cancer of the prostate. The occurrence of normal levels of "prostatic" acid phosphatase in a very few cases of prostatic cancer suggested the possibility that abnormal amounts of this enzyme could be induced to appear in the serum of such subjects if they were given small doses of testosterone (50 mg. three times a week). This proved to be so (Fig. 6). In several cases presenting difficult problems in the differential diagnosis of cancer of the prostate, this testosterone test provided the decisive evidence. In these patients, complete confirmation of the diagnosis of cancer was obtained some time later by biopsy or autopsy.

The ability of the tumor to respond to testosterone stimulation seems to depend upon its "activity." As shown in Figure 6, some patients respond by a marked

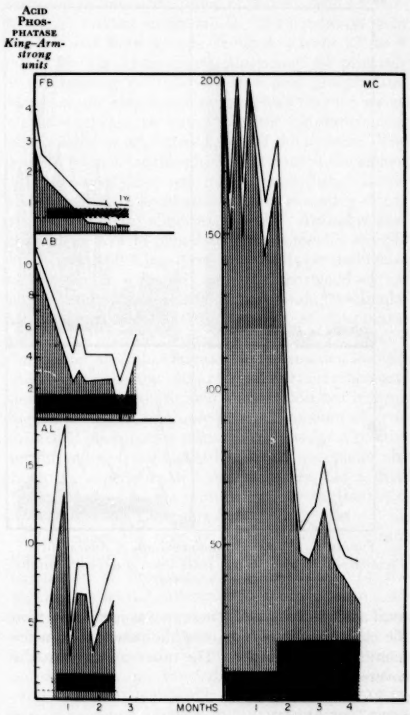

FIGURE 5. *Effects of Estrogen Therapy in Cancer of the Prostate.*

Stilbestrol dosage was 5 mg. a day for F.B., 10 mg. a day for A.L. and 15 mg. a day for A.B. chlorotrianisene (TACE) dosage for M.C. during the first period was 24 mg. a day and during the second period, 48 mg. a day. "Prostatic" data are shaded.

increase in serum enzyme activity. However, we have seen a patient (J.S.) with proved prostatic cancer whose serum "prostatic" acid phosphatase values remained continuously within normal limits and who responded to testosterone stimulation with only one abnormal value.

Cancer of the Breast

Two cases were discovered with elevated total serum acid phosphatase. These patients were in the late stages of metastatic breast cancer. Both showed a normal prostatic component in the serum. One of these subjects (Fig. 1) received cortisone therapy, which was accompanied by a reduction in the serum total acid phosphatase. Therapy was ineffective from the clinical point of view, and the patient died a few months after admission. The other subject was discovered in an earlier study.[1]

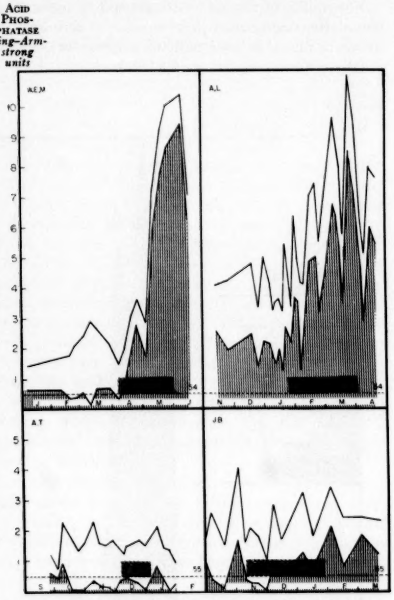

FIGURE 6. *Effects of Administration of Androgens. Testosterone dosage: 50 mg. three times a week. "Prostatic" data are shaded.*

Long-Term Studies

In 2 subjects with proved cancer of the prostate, estrogen therapy was interrupted and serum enzyme levels were followed regularly. In both patients there were rhythmic fluctuations in the serum prostatic acid phosphatase, 1 (Fig. 4) eventually reaching high levels, and the other (Fig. 7) returning to the normal range. These 2 cases demonstrate the interval between the finding of an abnormal serum prostatic acid phosphatase and the eventual appearance of the abnormal total acid phosphatase. It is interesting that patient C. B. died of cardiac failure and patient J. C. of his prostatic disease. These studies are perhaps the first to provide a picture of the natural course of prostatic cancer as followed by the serum prostatic acid phosphatase.

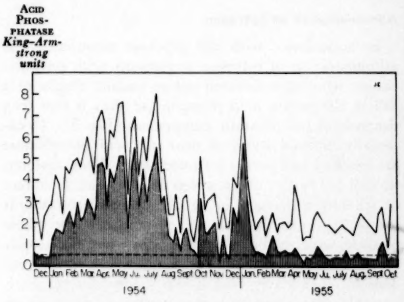
Acid Phosphatase King–Armstrong units
Dec. Jan. Feb. Mar. Apr. May Jn. July Aug. Sept. Oct. Nov. Dec. Jan. Feb. Mar. Apr. May Jn. July Aug. Sept. Oct.
1954
1955

FIGURE 7. *Long-Term Study of a Patient Admitted to the Hospital with Metastatic Cancer of the Prostate. No therapy was given except for a short period of cortisone administration as part of another study (July 26 to August 26, 1954). "Prostatic" data are shaded.*

Discussion

This paper is based on the proposition that an enzyme obtained from a given tissue may possess distinctive biochemical "marks of identification."

There is little doubt that the identification of the tissue source of an enzyme present in the serum has assumed great importance in medicine.[13] Thus, serum amylase elevations have been correlated with pancreatic and parotid-gland disorders, increased serum alkaline phosphatase with certain diseases of liver and bone, and, recently, a rise in serum transaminase with myocardial infarction. In some cases, however, the sources of the enzyme were highly specialized tissues that appear to be the sole producers of the enzyme (for example, amylase in the pancreas and parotid gland), or the nature of the disease was such that strikingly abnormal findings were usually encountered (for example, elevated serum alkaline phosphatase in obstructive jaundice and in benign and malignant bone disease).

However, with an enzyme that will enrich the serum only moderately and may originate from more than one tissue source, the identification of the organ providing this additional enzyme activity becomes difficult. This is the situation with serum acid phosphatase, whose level does not exceed 5.0 King–Armstrong units in 63 out of 91 cases of cancer of the prostate (Table 1) and which is known to be a mixture of acid phosphatases.

Regarding acid phosphatase, the properties of the crude enzyme from various tissues, although generally similar, exhibited certain striking differences. Thus, erythrocytic and splenic acid phosphatase hydrolyzed

alpha and beta glycerophosphates at distinctly different rates.[15] Ethanol inhibited prostatic but not erythrocytic acid phosphatase,[16,17] whereas formaldehyde inhibited erythrocytic acid phosphatase.[11] Erythrocytic acid phosphatase was sensitive to copper ion, unlike acid phosphatase prepared from other tissues.[1,11] L-tartrate inhibited acid phosphatase of prostate, liver, spleen and kidney but did not affect erythrocytic acid phosphatase. These and other differences of tissue extracts containing acid phosphatase are discussed in greater detail by Fishman and Davidson.[18]

Another example of an enzyme, preparations of which may show different properties from tissue to tissue, is beta glucuronidase.[19,20]

It appears profitable, if the present findings are accepted, for investigators to search for distinguishing characteristics of selected enzymes of various tissues because the utilization of this information for enzyme assay in serum should increase the clinical accuracy and also simplify greatly the interpretation of the findings.

Clinical Implications

The use of tartrate inhibition has markedly improved the clinical accuracy of the serum acid in prostatic cancer, a positive correlation occurring in 87 per cent of the untreated proved cases in contrast to the figure of 31 per cent obtained for total acid phosphatase. In addition the "prostatic" acid phosphatase was elevated much more often in patients with prostatic cancer at stages of the disease preceding metastatic spread to bone.

Abnormal "prostatic" acid phosphatase was also more frequent in patients with *probable* cancer of the prostate. In addition a new category of male subjects is evident. These patients exhibit *abnormal* "prostatic" acid phosphatase levels in the absence of clinical signs of prostatic cancer. It remains to be seen whether clinical manifestations of disease will appear later. The success of the follow-up study of these patients rests solely on the interest of co-operating urologists and internists outside this research group. Certainly, biopsy, examination of the prostatic smear for cancer cells and a testosterone stimulation test would constitute valid recommendations in these subjects.

Regarding the *borderline* group these symptomless patients (2.0 per cent of the total number of subjects) have on only one occasion shown a value for prostatic acid phosphatase between 0. 6 and 1.0 units. Many of them have been lost to follow-up study, and others have registered normal levels on subsequent analyses. It is possible that this group includes subjects who have undergone rectal examination before the taking of venous blood, an event that is known to elevate serum "prostatic" acid phosphatase in 50 per cent of men.[3] An appreciable number of these were younger patients seen in the venereal-disease clinic. So far no direct correlation has been observed between elevated serum acid phosphatase and inflammatory genitourinary disease or sexual activity. On the other hand laboratory error may be the explanation for some of these data although one cannot exclude the presence of a small prostatic cancer.

Low Values in Early and Advanced Cancer of the Prostate

A perplexing problem in the field of serum acid phosphatase and untreated cancer of the prostate concerns the existence of a group of patients who regularly exhibit normal serum values. The number of such patients has been greatly reduced — from 27 to 4 out of 39 (Fig. 2) by the introduction of the principle of determining L-tartrate-sensitive acid phosphatase. However, the conclusion is inescapable that the serum may not always be enriched with "prostatic" acid phosphatase in untreated cancer of the prostate. The possible reasons for this phenomenon merit discussion.

In the first place one may inquire "what is the amount of acid phosphatase protein necessary to enrich the blood to abnormal levels?" Assuming that pure prostatic acid phosphatase has a specific activity of around 4000 King–Armstrong units per milligram of phosphatase protein[21] and that the blood of the normal adult contains 2000 ml. of serum, the circulation need possess only 0.005 mg. of acid phosphatase protein to provide a serum registering 1.0 unit of "prostatic" acid phosphatase. No information is available concerning the rates of synthesis, excretion and destruction of prostatic acid phosphatase, but it seems logical to suggest that only a minute amount of prostatic acid phosphatase protein accounts for a positive serum value. This suggestion seems reasonable also from our experience and that of others that a small lesion localized to the prostate may be the source of increased serum acid phosphatase.

Next arises the question of the factors governing the exit from the gland and the entrance into the circulation of prostatic acid phosphatase. In this regard, the actual difference in specific enzyme activity between cancerous and normal prostatic tissue seems unimportant. Woodard[22] has found that the acid phosphatase activity of prostatic cancer tissue is no different from that of normal prostate and is *often* lower. It is probably not as a result of an excessive amount of enzyme in tumor that serum elevations appear. It appears, therefore, that certain unknown features of the structure of the neoplastic prostate favor the entrance of its acid phosphatase into the circulation.

The fact that there is no relation between acid phosphatase elevation and the amount or type of prostatic cancer in both localized and disseminated prostatic cancer is another point that calls attention to mechanisms of entry into the circulation of the biochemically specific component of this tumor, rather than tissue excess. It further suggests that the pros-

tate gland itself, rather than its cancer, is the main source of serum acid phosphatase when it harbors a tumor.

In this regard, it is interesting to consider a simple mechanical process for explaining the entrance of acid phosphatase from the cancerous prostate into the circulation. This concept is based on the observation that massage of the prostate gland is often followed by a transient but notable rise in the serum "prostatic" acid phosphatase in patients with and without cancer of the prostate. In the patient with a small cancerous nodule the elevated serum "prostatic" acid phosphatase may be due to mechanical pressure on or to "plugging" of the orifices of the normal gland, whose phosphatase may then readily "back up" into the blood stream. It seems improbable that the tumor itself is responsible, for the reasons stated earlier. It is conceivable that mechanical pressure may be intermittent, especially in early stages of prostatic cancer, because structures adjacent to the prostate gland and its tumor gradually adjust to its growth. Consequently, there may be periods when a small tumor does not compress the adjacent normal tissue areas. The occurrence of an appreciable number of abnormal "prostatic" fractions in the serum of patients with benign prostatic hypertrophy may thus be due to pressure by growing intraglandular fibrous tissue.

On the other hand, in metastatic cancer of the prostate, the metastatic tissue would represent an additional large source of enzyme, but the movements of this enzyme would be under the control of a set of circumstances — for example, degree of necrosis and extent of blood supply — different from the ones visualized in the localized lesion.

The possible role of serum inhibitors and activators, heat inactivation and transferase phenomena have been mentioned as explanations for normal serum phosphatase levels in prostatic cancer. These are discussed elsewhere.[18]

Summary and Conclusions

A total of 91 proved cases of cancer of the prostate and 1175 patients without this disease were investigated for serum acid phosphatase levels.

In all these cases determinations were performed for total and "prostatic" acid phosphatase, the substrate, phenyl phosphate, being used.

It was found that the Fishman–Lerner method gave the best correlation with the presence of proved cancer of the prostate, registering 87 and 81 per cent abnormal in untreated and treated cases respectively. The corresponding figures for total acid phosphatase were 31 and 38 per cent.

The Fishman–Lerner method indicated abnormal "prostatic" acid phosphatase values more frequently than the King–Armstrong method in the cases in which prostatic cancer was localized to the gland (21 out of 26) and when metastases had spread only to soft tissue (11 out of 12). The corresponding figures by the King–Armstrong procedure were 4 in 26 and 2 in 12. Likewise, in the group with bony metastases, the Fishman–Lerner method was more sensitive, showing abnormal phosphatase values in 45 of 53 patients as compared to 25 out of 53 found with the King–Armstrong procedure. Accordingly, an elevated "prostatic" acid phosphatase is not necessarily an indication of metastatic as opposed to nonmetastatic cancer of the prostate.

The effect of cessation of estrogen therapy in prostatic cancer was followed by a rise in serum "prostatic" acid phosphatase in some patients and not in others.

Estrogen therapy induced a characteristic fall in serum acid phosphatase that was due to a decrease in the tartrate-sensitive moiety.

In selected cases, the administration of androgen produced a subsequent rise in "prostatic" acid phosphatase, an event which can be of practical importance in diagnosis.

Long-term studies (two years) on prostatic cancer showed in detail the course of the serum acid phosphatase.

A study of the clinical specificity of the serum "prostatic" acid phosphatase showed that prostate cancer only exhibited persistent abnormal values; the most frequent occurrence of abnormal values in nonneoplastic disease was seen in benign prostatic hypertrophy (15 of 52 cases). The strong possibility that some of these patients have occult cancer of the prostate cannot be excluded.

Elevated total acid phosphatase levels were observed in 2 women with cancer of the breast. The "prostatic" fraction was normal.

The clinical value of the "prostatic" acid phosphatase is discussed in relation to the earlier diagnosis of cancer of the prostate, and the thesis of identifying the tissue source of a given enzyme by the use of a specific inhibitor is stated.

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CURRENT TREATMENT OF INFANTILE HYDROCEPHALUS*

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PARENTS of an infant with internal hydrocephalus are interested, whether or not they are aware of it or admit it to themselves, not in survival of their child but in a chance for normal development. Although danger to the child's life itself may be the first problem such parents face, it soon becomes apparent that the possibility of sustaining a hopeless defective may be a much more devastating tragedy.

From the surgeon's point of view, there is certainly little incentive to perform operations that permit life to go on but do not allow cerebral growth and development to proceed at a normal rate. To carry out such procedures knowingly is to fail to act in the best interests of the patient, his family and his community. In their efforts to relieve suffering, physicians must be wary constantly that they do not simply prolong it. The chief concern, therefore, has been to select hydrocephalic children in whom clinical judgment, as well as objective measurements, indicates that normal development is reasonably possible, and to carry out, as early as feasible, an operation that will consistently maintain normal intracranial pressure.

It is my belief that every hydrocephalic infant should have sufficient clinical and laboratory evaluation so that the surgeon can make definitive and authoritative recommendations to the family and the referring physician. One of three decisions should be reached; although this decision may occasionally be made with reservations in the surgeon's mind, it should be conclusive as far as the family is concerned.

In the first place the family should be told that progressive hydrocephalus is present but evidence of irreversible brain damage is lacking and therefore that the best available surgical procedure to restore spinal-fluid circulation to normal in the type of hydrocephalus present should be carried out as soon as possible.

The second decision that may be evident is that irreversible central-nervous-system damage is unquestionably present to a degree that prevents an acceptable result no matter how successful operative treatment of spinal-fluid obstruction may be, and therefore custodial care only should be considered, whether at home or in an institution. It is here that the doctor's and the parent's responsibility is to see that suffering is minimized but not prolonged.

The third alternative is that although hydrocephalus is present, there is no definite evidence that it is actively progressive at the time of examination. Under these circumstances, a definite program of repeated, regular checkups should be scheduled, not as procrastination but as a planned form of treatment to determine whether or not there is increased intracranial pressure or an accelerated rate of head growth and therefore need for subsequent surgical therapy. Arriving at one of these three decisions is essential in every patient.

Progression of hydrocephalus is most accurately assessed by regular estimation of intracranial pressure and by regular measurement of the occipitobregmatic head circumference. It should be remembered that if an infant's head is already enlarged, it will not grow at all for a while if intracranial pressure becomes normal; it will wait until the body catches up. If the enlarged head continues to grow, therefore, even though slowly, it means that there is still increased intracranial pressure.

It would be most gratifying to report some startling new methods and radically improved results in the treatment of infantile hydrocephalus. Unfortunately, this problem remains a most frustrating and at the same time a most challenging one. Although current

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methods of treatment represent a considerable advance over those available a decade ago, they must still be considered for the most part unsatisfactory. Surgeons have not yet learned to substitute any mechanism that can replace the normal reabsorption of cerebrospinal fluid into the circulating blood through the diffuse vascular network of the pia arachnoid investing the brain's surface.

It is useful to remember that the brain and spinal cord are normally surrounded by a series of connected spaces containing cerebrospinal fluid and that this fluid is constantly being produced and reabsorbed. The physiology of hydrocephalus is concerned primarily not with the site of formation, or the rate of formation of cerebrospinal fluid, but rather with its access to and rate of reabsorption from these subarachnoid pathways investing the surface of the brain. Unless spinal fluid is removed at a normal rate from these surface pathways it will in time accumulate and cause increased pressure, no matter where or at what rate it continues to be formed.

Efforts to alter the rate of formation of cerebrospinal fluid by medical or surgical means have never achieved any significant measure of success, certainly not in the presence of severe degrees of failure of spinal-fluid absorption. In the present state of knowledge, therefore, attempts at diversion of spinal fluid to a surface of excretion from the body or a surface where reabsorption can progress at a rate comparable to that of the normal pia arachnoid continue to be the best methods available. No attempt is made in this brief report to review the history of cerebrospinal-fluid shunting procedures. Likewise, no attempt is made to describe or analyze the clinical results achieved by the many surgeons interested in this problem. This should rather be considered in the nature of a progress report from one clinic.

My own experience with this problem in the last eight years, disregarding earlier abortive maneuvers, includes spinal-fluid shunting operations of one kind or another in 210 patients. In these patients, a total of 379 separate operative procedures have been performed. This group can be broken down as indicated below.

Lumbar Ureteroarachnoid Shunts

In this operation spinal fluid is shunted through a plastic tube from the lumbar spinal subarachnoid space into the ureter after removal of a kidney. It is obviously applicable only to communicating hydrocephalus.[1,2] This operation has been performed in 108 patients and has given by far the most satisfactory long-term results of any type of shunting operation. There is virtually no operative mortality to this procedure (less than 1 per cent). Complications have been of three types:

Meningitis secondary to urinary infection, which has occurred in 6 to 8 per cent of the group and has been fatal in 3 per cent.

Mechanical obstruction of the tube, which has been rare and always correctable by replacement of the tube; 18 of the 108 patients in this group have required a secondary operation, usually for mechanical reasons.

Acute dehydration due to fluid and electrolyte losses through the shunt during periods of inadequate intake secondary to intercurrent infections; this has been a serious problem, but it can be prevented or successfully treated in almost every case if the child's parents and the pediatrician are sufficiently warned.

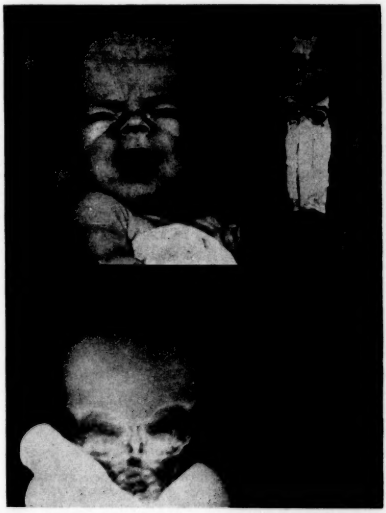

Figure 1. *Progress of a Child with Hydrocephalus.*
Upper left=appearance at six weeks of age, when the infant, who weighed 3.2 kg. (7 pounds), had a greatly enlarged head.
Lower left=ventricular air-bubble study (before lumbar-arachnoid-ureteral shunt), indicating the severe degree of ventricular enlargement.
Right=appearance six years after operation, showing a normal head size. Neurologic examination was negative. The child's mental and motor development are at a normal level for his age.

Between 60 and 70 per cent of children who have had this procedure are alive, and, what is much more important, with few exceptions those who survived are asymptomatic and developing well for periods from a few months up to over seven years. These are all children who had proved severe progressive hydrocephalus — children who would otherwise be dead or hopelessly damaged by this time (Fig. 1 and 2).

Ventriculoureteral Shunts

Ventriculoureteral shunts have been performed 69 times in 46 patients with obstructive hydrocephalus. This operation, which consists in shunting fluid from a lateral ventricle through a long subcutaneous tube to the ureter, is easy to do and for short periods works very well.[3] It is unsatisfactory from a long-term point of view because of the necessity for lengthening the tube with growth of the child — usually every twelve to eighteen months. The long course of the tube subjects it to many possibilities for mechanical failure. This operation is no longer performed if other procedures can be made effective.

Figure 2. *Progress of Another Child with Hydrocephalus. Upper left=appearance at four and a half months showing the enlarged head and markedly increased intracranial pressure. Lower left=preoperative ventricular air-bubble study, showing the severe degree of ventricular enlargement. Right=appearance seven years after lumbar-arachnoid-ureteral shunt. The child has received superior marks in second grade, does tap and ballet dancing and is a well poised, attractive youngster.*

Peritoneal Shunts

Peritoneal shunts — that is, fluid diversion through plastic or rubber catheters from the lateral ventricle or from the lumbar subarachnoid space to the peritoneal cavity at a variety of sites — have been carried out 155 times in 64 patients.[4,5] The large number of operations in proportion to the number of patients reflects the difficulties encountered in this clinic in making these shunts function satisfactorily. The technical problems associated with keeping the peritoneal end of such shunts patent are legion, and although an occasional shunt works well from the beginning, the over-all percentage is discouragingly meager. This method is largely being employed for patients in whom drainage into the urinary tract is not suitable — for example, those with hydrocephalus secondary to the Arnold–Chiari malformation and spina bifida.

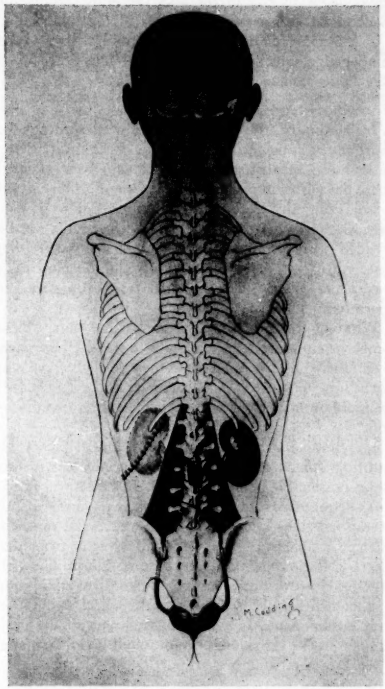

Figure 3. *Combined Ventriculocervical and Lumbar-Arachnoid-Ureteral Shunts in the Treatment of Obstructive Hydrocephalus.*

Ventriculocervical Shunts

The routine Torkildsen operation, or ventriculocisternostomy, has been found to be unsatisfactory in infants less than six months of age. Recently, instead of this operation, a shunt has been performed through a rubber catheter from the lateral ventricle of the brain into the subarachnoid space anterior to the upper cervical spinal cord. In this procedure a hemilaminectomy of the second and possibly the third cervical segment is carried out through a very limited exposure. The posterior fossa of the skull is not opened at all, greatly simplifying the procedure in small infants. This operation has been performed 38 times in 31 patients in the past two years. In a few

patients it has satisfactorily relieved the hydrocephalus by itself. In most cases, however, it has merely converted an obstructive into a communicating hydrocephalus, which is treated a week to ten days later by lumbar-arachnoid-ureteral shunt. This combination of shunts eliminates the long tube from the ventricle down to the ureter and therefore avoids the mechanical and growth problems of the latter (Fig. 3). A number of these double shunts have now been in operation satisfactorily for more than a year.

Discussion

In summary the only significant percentage of satisfactory long-term results has been in patients with shunts into the urinary tract who have escaped acute dehydration and infection. One must be careful in analyzing any treatment for hydrocephalus to rule out cases of spontaneous arrest, and one must not be satisfied with a child who is simply kept alive; the child must be permitted to grow and develop at a normal or nearly normal rate from the time of operation.

What of the future? It seems to me that, unless some revolutionary and radically different approach to infantile hydrocephalus comes to light, or one learns how to prevent its occurrence in the first place, the most promising fields of endeavor lie in two directions.

The first is improvement of the technical aspects of shunting spinal fluid into the peritoneal cavity so that a reasonable percentage of such shunts will function adequately from the beginning, with no need for alteration. This aim can probably never be reached when it is necessary to shunt fluid directly from the ventricle in young infants because of the problem of growth. However, any shunt that can divert fluid into a space where it can be reabsorbed and avoid the problems of acute dehydration inherent in ureteral shunts must be considered preferable if it can be made to work in a satisfactory proportion of patients.

The second line of endeavor seems to be in the development of some kind of artificial valve to permit absolutely competent unidirectional flow of fluid from the lateral ventricles of the brain directly into the circulating blood stream, no matter what the pressures in the ventricle or venous system might be. In this clinic, as well as in others, investigation of valves of small caliber is being carried out; this work has proceeded to the stage of considerable enthusiasm and cautious optimism, but as yet there are no reportable results.

Conclusions

The ideal operation for hydrocephalus should fulfill the following requirements: it should be standard and simple enough for any good surgeon to perform; it should be applicable to all types of hydrocephalus, regardless of the site of cerebrospinal-fluid obstruction or the age of the patient; it should not be influenced by normal growth or any other conditions that would necessitate repeated operations; and it should, of course, allow a high percentage of patients to achieve not only immediate but also permanent reduction of increased intracranial pressure to normal levels.

Though weary of many disappointments, I am still optimistic enough to believe that the next decade will see considerably more progress in this field than has occurred in the last.

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FAMILIAL OCCURRENCE OF DISSEMINATED LUPUS ERYTHEMATOSUS*

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ONLY a few cases of the familial occurrence of disseminated lupus erythematosus have been reported in the literature. This report is concerned with the observation of disseminated lupus erythematosus occurring in both mother and daughter.

Case Reports

Case 1. J.K., a 44-year-old housewife, was admitted to the Beth-El Hospital on September 4, 1953. She had emigrated from Russia at the age of 2. Her mother had died of a "stroke" at 65, and her father of a heart attack at 64 years of age. Two sisters were living and well. One brother had had rheumatic fever and hay fever. She had had 2 pregnancies, with 2 living children. A hysterectomy and salpingo-oöphorectomy had been performed in 1944 at the age of 39.

She had suffered repeated attacks of thrombophlebitis in both legs since the birth of her 1st child 23 years previously, associated with varicose ulcers during the past 6 months. These generally subsided with bed rest and topical applications. Between October 7 and October 21, 1948, an exacerbation of the phlebitis had been treated with heparin and Dicumarol. No cutaneous lesions were observed at that time, and the white-cell count was within normal limits.

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She had experienced tingling paresthesias of the fingers for the last 20 years. During the 5 years before admission she had been suffering from left-sided fronto-occipital headaches each day, relieved by 2 "B.C." tablets and associated with mild dizziness, diplopia, scotomas and photophobia. A morning cough productive of foul-smelling sputum was present during the same period.

During the summer of 1948, while on vacation, she experienced a sudden, marked swelling of the face, which subsided in 3 days. In the course of the next year, mild, intermittent pains in the left wrist and hand set in. A 2d episode of diffuse erythematous swelling of the face occurred in August, 1949. At the same time an increasing dryness of the throat developed, with dysphagia, a weight loss of 5.9 kg. (13 pounds), intermittent nausea and vomiting, polyuria, nocturia, frequency and urgency. The facial swelling subsided in 3 or 4 days. A few weeks later she "took a sun-lamp treatment" at a beauty shop. Three or four hours after exposure the swelling of the face returned, and a spotty, burning pruritic rash appeared on the neck and chest. The rash became more diffuse and painful, and eventually pustular, excoriated and bleeding. The joint pains in the wrist and hand had become intense. The neck lesions did not change, but the facial swelling subsided completely.

In November discrete, erythematous, pruritic, maculopapular lesions appeared over the nasolabial folds, gradually spreading to the malar regions and the bridge of the nose. She was admitted to another hospital in December, when physical examination revealed a well developed, well nourished woman in moderate distress. Her hair was dyed, and her scalp somewhat erythematous. Enlarged (1 or 2 cm.) submandibular, anterior cervical and axillary lymph nodes were palpated. A blowing systolic murmur was heard at the apex together with a split 1st sound at both the apex and the base. The blood pressure was 108/72, the pulse 88, and the temperature 99°F.

The skin of the neck, the anterior aspect of the chest, the back, the shoulders and the upper arms was covered by a pustular rash, and a discrete, macular, erythematous eruption was present on the skin of the malar areas and the bridge of the nose. There was some dryness of the skin of the forearms and an erythematous, hot, indurated, tender, hyperpigmented area over the left calf.

Examination of the blood showed a red-cell count of 3,700,000, with a hemoglobin of 11.7 gm. per 100 ml., and a white-cell count of 3350, with 19 per cent stab forms, 54 per cent segmented neutrophils, 1 per cent eosinophils, 20 per cent lymphocytes and 6 per cent monocytes. Platelets numbered 180,000. Subsequent white-cell counts varied from 2900 to 6000, with the majority under 5000. Repeated determinations of the sedimentation rate ranged from 55 to 106 mm. per hour. The blood sugar was 95 mg., blood urea nitrogen 11 mg., alkaline phosphatase 4 King–Armstrong units, serum bilirubin 0.2 mg., total cholesterol 500 mg., cholesterol esters 350 mg., albumin 4.1 gm., and globulin 3.6 gm. per 100 ml. A formol-gel test was +, and cephalin flocculation +. Blood cultures were negative. The urine contained a trace of albumin, with an occasional white cell in the sediment and no porphyrins.

Bone-marrow aspiration revealed a cellular marrow. No L.E. cells were found in preparations made from the buffy coat of the marrow or of the peripheral blood. Skin and muscle biopsies disclosed changes consistent with chronic discoid lupus erythematosus. An electrocardiogram and an x-ray film of the chest showed no abnormalities. The patient was given intramuscular injections of procaine penicillin along with topical applications (boric acid ointment) to skin lesions. The infection cleared within 2 weeks, leaving an erythematous, macular lesion. The hospital course was afebrile except for 1 rise in temperature to 101.4°F. during the 2d hospital week, when right-sided pleuritic pain and a right-sided pleural effusion, with infiltration at the right cardiophrenic angle, developed. Thoracentesis revealed yellow, cloudy fluid containing 40,000 white cells per cubic millimeter, with 60 per cent polymorphonuclear leukocytes, macrophages and mesothelial cells. The specific gravity was 1.024; the Rivalta reaction was positive. A gram stain and acid-fast smears were both negative. Chlortetracycline and penicillin were given, and the effusion cleared within 2 weeks. The thrombophlebitis subsided after treatment with Dicumarol.

During most of 1950 the patient was seen in the outpatient department of another institution at frequent intervals. The cutaneous lesions remained localized to the areas previously described. She complained of pains and stiffness of the interphalangeal joints, which appeared somewhat spindle shaped. She gained some weight and remained afebrile; examination of the blood revealed a red-cell count of 3,700,000 with a hemoglobin of 11.4 gm. per 100 ml., and white-cell counts of 3000 to 5200, with 54 per cent segmented neutrophils, 43 per cent lymphocytes, 2 per cent eosinophils and 1 per cent monocytes. The sedimentation rate was elevated to 62 mm. per hour.

She was readmitted to the hospital from May 31 to July 5, 1951, for another exacerbation of the thrombophlebitis of the left leg. Clinical and laboratory findings were similar to those of previous admissions, and L.E. cells were demonstrated in the peripheral blood. Her general condition improved during the hospital stay.

There were 2 subsequent hospital admissions to other institutions from July 26 to August 6, 1952, and from March 21 to April 29, 1953, for recurrent thrombophlebitis ("diffuse erythematous lesions" on the left leg). During the 2d of these admissions excoriated buccal lesions were observed. A saphenous-vein ligation was performed.

The last hospital admission was to the Beth-El Hospital on September 4, 1953, with the complaint of bilateral erythema, swelling and pain in the legs, more marked on the left. There were bilateral buccal lesions, compatible with the diagnosis of lupus erythematosus.

The temperature was 99.8°F., and the pulse 72. The blood pressure was 160/40.

Examination of the blood showed a red-cell count of 3,600,000, with a hemoglobin of 10.5 gm. per 100 ml., and a white-cell count of 4800, with 2 per cent stab forms, 54 per cent segmented neutrophils, 43 per cent lymphocytes and 1 per cent monocytes. The sedimentation rate was 28 mm. per hour. L.E.-cell preparations were again positive. The Mazzini test was negative. The albumin was 4.2 gm., and the globulin 3.9 gm. per 100 ml. Urinalyses were repeatedly negative, and the maximum specific gravity was 1.024. Phenolsulfonphthalein excretion was slightly below normal limits. Treatment with ACTH was instituted, and the buccal lesions seemed to recede. The blood pressure at this time was 140/70.

On October 18 ACTH was stopped for fear of aggravating incipient abscesses of the buttock. The buccal lesions subsequently reappeared, and an episode of chills and fever (temperature of 103.4°F.) occurred on October 22d. There was a fall in blood pressure to 110/60, and the pulse rate rose to 112. Oxytetracycline, aspirin and an alcohol sponge were unavailing, and the temperature rose to 105°F. Cortisone, heparin, Benadryl and Pyribenzamine were given, but diarrhea set in and the patient lapsed into coma on October 26, with nuchal rigidity, ankle clonus and hyperesthesia. She died with bleeding from the buccal mucosa.

Case 2. R.K., an 18-year-old girl (the daughter of the patient in Case 1), was admitted to this institution complaining of cough, lip sores and fever on February 13, 1954. She had been well until 3 weeks previously, when she visited her physician because of pain and stiffness in the shoulders and back, a feeling of fatigue and painful fissures of the lips. Bed rest brought no relief, and after returning to work for 2 days, she was forced to return to bed because of stiffness and pain in the knee joints. Subsequently, similar symptoms appeared at the elbow and finger joints, associated with a productive cough and a high fever. A week before admission she was unable to leave her bed, and the temperature reached 106°F. During this week she was given antibiotics for "pneumonia" without response and then admitted to the hospital. She stated that she had lost 3.6 kg. (8 pounds) since the onset of her illness, and that the menstrual period preceding her illness had been unusually delayed and accompanied by pain in the lower abdomen. Her rusty-red hair had always been sparse, and her skin extremely sensitive to light, often blistering on exposure.

The past history revealed a sore throat at the age of 14, and she stated that a "V"-shaped, red "rash" appeared on the neck during periods of stress. Her father had died of hypertensive cardiovascular disease at the age of 42, and a 24-year-old brother was said to have had rheumatic fever.

Physical examination revealed an acutely ill, slightly obese young woman with a flushed but fair complexion. Ill defined erythematous maculae were present on the forehead, nose and right breast. The conjunctivas were clear, but the scleras were mildly injected. The lips were dry and scaly. She coughed and expectorated whitish sputum. Examination of the chest revealed dullness to percussion over the left base and axilla, with diminution of breath sounds and occasional post-tussal rales in these areas.

The temperature was 101°F., and the pulse 100. The blood pressure was 130/76.

X-ray study confirmed the presence of a pneumonic process at the left base. Laboratory findings consisted of a ++ test for albumin, poor power of urinary concentration and normal phenolsulfonphthalein excretion. The hemoglobin was 11 gm. per 100 ml., and the white-cell count 5000, with 12 per cent stab forms, 28 per cent segmented neutrophils and 56 per cent lymphocytes. The sedimentation rate was 24 mm. per hour (Wintrobe method), and abundant L.E. cells were demonstrated by the clot method. The fasting blood sugar was 100 mg., the blood urea nitrogen 13.1 mg., the albumin 3.4 gm., the globulin 3.9 gm., the serum bilirubin 0.17 mg. total and 0.4 mg. indirect and the alkaline phosphatase 4.9 King–Armstrong units. Cephalin flocculation was ++++, and thymol turbidity 8.5 units.

On the 4th hospital day painful ulcerated areas were found on the oral and pharyngeal mucous membranes. On the following day macular erythematous patches about 1 cm. in diameter appeared on the dorsa of the hands and on the forearms. The patient complained of blurred vision. The ocular fundi were slightly edematous, and the disk margins blurred, and fluffy exudates were present. Chemosis and palpebral edema were also noted.

ACTH therapy was begun on the 7th hospital day, with rapid subjective and objective improvement. The hand and forearm lesions disappeared, appetite and vision improved, expectoration increased, and the thoracic findings receded. The temperature dropped to 100°F., and the buccal ulcerations improved. The ACTH was discontinued after 2 weeks because the face had become moon shaped. This treatment was reinstated 4 days later, for the ulcerated lesions of the mucous membranes had recurred. Cortisone was eventually substituted for ACTH. Improvement was continuous and marked after this, the lung and mucous-membrane findings clearing entirely. The eye grounds did not change on subsequent examination. By the time of discharge, 38 days after admission, all initial symptoms had either disappeared or improved. The patient still complained of headache. The white-cell and differential counts approached normal, although L.E. cells were still abundant. Urinalysis was unchanged.

After a month of well-being she began to feel weak once again. She had been seen weekly, and cortisone had been discontinued 5 days before the second admission, when swelling of the eyelids was observed. She had lost 5.4 kg. (12 pounds) between admissions.

On readmission on June 25 she had a puffy facies, edematous eyelids, chemosis and slight pedal edema; the blood pressure was 124/80. Petechiae were visible on the hard palate, and the gingivae were spongy, bleeding easily on contact. ACTH was given, and most of the symptoms and signs receded, though articular stiffness and pain appeared for several days during the hospital stay. She was discharged on cortisone therapy. Repeated urinalyses showed ++ to ++++ tests for albumin, and the sediment contained many white blood cells in clumps. The hemoglobin averaged 9 gm. per 100 ml., and white-cell counts varied from 5050 to 11,200, with a slight relative lymphocytosis. The globulin fraction of the serum was consistently high; cephalin flocculation was ++++, and thymol turbidity 15 units. No L.E. cells could be demonstrated.

After discharge she complained of occasional headaches, dizziness and pains in the phalangeal joints. She was observed in the hospital overnight on August 19, but no new physical findings were elicited.

She was admitted to the hospital for the 4th time on September 11, with a temperature of 103.2°F., and treated for a genitourinary-tract infection, which responded quickly to antibiotics; the blood pressure at that time was 142/80. Albuminuria was still marked. The hemoglobin was 9.5 gm. per 100 ml., and the white-cell count 11,000, with a shift to the left. The blood sugar, blood urea nitrogen and albumin-globulin ratio were within normal limits and again no L.E. cells were demonstrated. A chest film revealed no abnormalities. She was discharged on September 18, only to be readmitted to the hospital with an upper respiratory infection and fever (temperature of 103°F.), which again responded to antibiotics. Intravenous pyelography revealed some atypical configuration of the calyceal system on the left, and by the time of discharge on October 12, the white-cell count was 4650, with 45 per cent segmented and 11 per cent nonsegmented neutrophils, 3 per cent eosinophils, 34 per cent lymphocytes and 7 per cent monocytes. The serum albumin and globulin were 3.5 and 3.2 gm. per 100 ml. respectively.

The patient was admitted to the hospital for the last time on November 1. Treated daily with infusions of ACTH, she had been subjectively quite well until the morning of admission, when she was found foaming at the mouth and difficult to rouse. She was semicomatose at the time of admission, and during examination had a Jacksonian seizure with convulsive movements of the right upper and lower extremities and deviation of head and eyes to the right. There were several seizures subsequently, but she eventually regained consciousness. A residual right-sided hemiplegia with nuchal rigidity was observed, and the cerebrospinal fluid was xanthochromic. An intracerebral hemorrhage, subsequent to cerebral lesions of disseminated lupus erythematosus, was considered to be the underlying cause. On the 9th hospital day many macular patches of erythema, about 1 cm. in diameter, were observed on the chest, arms and abdomen. These vanished on the following day, and physiotherapy was instituted although she remained somewhat disoriented and unco-operative.

On the 18th hospital day she once more had several successive seizures and lapsed into coma. She remained in coma and died on the 22d hospital day.

Until the final episode the blood pressure was elevated (170/100), and laboratory findings were not different from those on previous admissions except for a moderate leukocytosis (white-cell count of 18,000) and an elevated blood urea nitrogen.

Post-mortem examination revealed onion-skin-like layering of the collagen surrounding the arteries of the malpighian bodies of the spleen. Kidney sections showed mucinous wire-loop lesions, thickening of Bowman's capsule with adhesions to the tufts and areas of fibrinoid necrosis. Foci of chronic interstitial inflammation and hyaline casts were also present. The skin showed thinning of the epidermis, with atrophy of the rete pegs, and an increase in the collagenous tissue of the dermis. Examination of the brain and meninges revealed complete thrombosis of the dural vessels and the superior sagittal sinus. A large hemorrhage was present in the left temporoparietal region. In addition, diffuse necrotizing arteriolitis and petechial hemorrhages were found throughout the cerebral parenchyma. Lung sections showed areas of emphysema, moderate congestion, edema and patches of pneumonia. No hematoxylin bodies were found. The diagnosis was disseminated lupus erythematosus.

Discussion

Although permission for autopsy was not granted in Case 1, the symptoms and course of the disease were sufficiently clear cut for this to be considered a case of disseminated lupus erythematosus within the current criteria of classification.[1] The patient exhibited weight loss, terminal hyperpyrexia, typical cutaneous lesions, with butterfly pattern and photosensitivity, typical mucous-membrane lesions, arthralgias, generalized lymph-node enlargement, nausea and vomiting, terminal central-nervous-system lesions, positive skin and muscle biopsies, leukopenia, some reduction of thrombocytes, anemia, elevated serum globulin and repeated demonstration of L.E. cells in the peripheral blood.

The daughter's clinical course was equally characteristic, and, like her mother, she manifested weight loss, hyperpyrexia, typical cutaneous and mucous-membrane lesions, photosensitivity, arthralgias, terminal central-nervous-system lesions, leukopenia, anemia, elevated serum globulin and L.E. cells. In addition the daughter had ocular and renal findings, and her clinical course was much more rapid.

Of the 5 previously reported cases of familial occurrence of disseminated lupus erythematosus only 3 are sufficiently well documented to be considered acceptable examples. One is the report by Tikhonov-Bugrov[2] of the acute fatal form in a brother and sister, both cases confirmed by autopsy. Another is reported by Davis and Gutridge[3] in identical twin sisters, confirmed by the post-mortem examination of 1. The third, in a mother and son, both confirmed by post-mortem examination, is reported by Pirofsky and Shearn.[4] Of the 2 others, 1 occurred in a father and daughter, but the clinical description is brief and no autopsy findings are provided[5]; 1 is a report in which 2 girls, who were third cousins, presented highly suggestive clinical and post-mortem findings.[6]

Other reports are available in which 1 patient presented characteristic lesions of disseminated lupus erythematosus and a sibling suffered from another disease that may or may not have been related to lupus erythematosus. One author describes a woman with disseminated lupus erythematosus whose sibling suffered from thrombotic thrombocytopenic purpura.[7] Another report mentions the occurrence of subacute lupus erythematosus in a man and chronic discoid lupus erythematosus in his sister, who never presented acute manifestations.[8] Scleroderma in the daughter of a woman with disseminated lupus erythematosus has also been observed.[9]

The remaining reported familial cases include only descriptions of skin lesions without systemic manifestations occurring in members of the same family. These have been enumerated by several authors.[1,4]

The etiology and pathogenesis of disseminated lupus erythematosus remain obscure despite recent advances in diagnostic and histologic technics. Infectious agents have been implicated either by direct action or by the establishment of vascular allergic manifestations through an infectious-allergic mechanism.[10,11] No single infectious agent has been satisfactorily or repeatedly demonstrated, although considerable evidence has been accumulated for an allergic hypersensitive hypothesis.[12] In animal experiments lesions similar to lupus erythematosus have been observed after anaphylactic hypersensitization to foreign proteins.[13] Human cases that seem to have been related to antitoxin and drug administration[14,15] lend support to this concept. It has been suggested that skin-localized lupus erythematosus occurs when systemic resistance is maintained and that the more severe systemic variant represents a failure of the immune mechanism.[16] Other authors are of the opinion that systemic lupus erythematosus is based on an antigen-antibody reaction whereas discoid lupus is a cutaneous hypersensitivity reaction to an infective focus.[17]

Hormonal imbalance and dysfunction have also been implicated, usually on the grounds of frequent occurrence of lupus erythematosus in women of childbearing age.[18,19]

An additional support for an antigen-antibody mechanism is found in the report of decreased serum complement in 27 patients with disseminated lupus erythematosus.[20] The same phenomenon has been demonstrated in children with the disease.[21]

An important recent observation is that of Bridge and Foley,[22] who describe the placental transfer of a serum factor related to L.E.-cell formation from a patient suffering with disseminated lupus erythematosus to her newborn infant. The mother had been ill for two years but was asymptomatic during her pregnancy, receiving steroid therapy throughout. The L.E.-cell phenomenon was unequivocal in the baby for seven weeks after delivery, but had disappeared by the age of four months. The authors note that the serum L.E. factor has been demonstrated to be part of the gamma-globulin fraction. The gamma-globulin fraction of patients with lupus erythematosus is capable of producing antibodies in rabbits that precipitate the L.E. factor. In the case presented by Bridge and Foley no such antibodies could be demonstrated. These findings do not imply that the child had or would later have disseminated lupus erythematosus. Although there is no evidence that the L.E. factor is the same gamma globulin as has been related to the characteristic ground-substance changes, it is possible that the lack of clinical findings in the infant was due to the dilution of the fraction and the normal limitations of the immune reactions of children.

In the cases reported above, the mother was menopausal (surgical) at the time of onset of her symptoms, and there is no evidence that any clinical manifestations were present either before or during her pregnancies. The daughter, however, gave a history of long-standing photosensitivity and the appearance of a "V"-shaped rash under stress.

If any link is to be established between the occasionally reported familial occurrence of the disease and the demonstrated placental transfer of the serum L.E. factor, studies of pertinent cases will have to be more numerous and include long-range observation of the offspring. It is perhaps noteworthy that in the cases presented above, there are striking similarities of symptomatology, especially in the terminal central-nervous-system manifestations with nuchal rigidity and coma.

To add to the numerous speculations about the etiology of disseminated lupus erythematosus, the following possible mechanisms may be mentioned. Transplacental transmission of antigenetic substances could provoke enough antibody formation in the fetus

to induce and eventually to sustain an anaphylactic sensitivity to a protein of otherwise limited reactivity.

On the other hand the antibody gamma-globulin fraction thought to be related to L.E.-cell formation could itself be transmitted, sensitizing the fetus to some ubiquitous antigen. Latency could be a function of the necessity for repeated contact with the antigen. Investigation of serum complement levels and electrophoretic patterns in parents, children and siblings of patients with disseminated lupus erythematosus are planned in an attempt to demonstrate possible subclinical immunologic manifestations of the disease.

Summary

Two cases of disseminated lupus erythematosus in the same family (mother and daughter) are presented. Both were clinically characteristic and included repeated demonstrations of L.E. cells. One was confirmed by autopsy.

A possible relation between familial occurrence of disseminated lupus erythematosus and placental transmission of the L.E.-cell factor is discussed.

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RADIOGRAPHIC VISUALIZATION OF MULTIPLE DIVERTICULA OF THE GALL BLADDER

Report of Three Cases

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NEW HAVEN AND WEST HAVEN, CONNECTICUT

THE radiographic demonstration of diverticula of the gall bladder is uncommon. However, in a review of 175 post-mortem cases, Robertson and Ferguson[1] found that 81 per cent of diseased gall bladders had diverticula, whereas 42 per cent of those without evidence of disease had diverticula that were shallower and fewer in number. The anatomic development of these diverticula and their more frequent occurrence in diseased organs created a controversy in the literature from the time they were first adequately described by Rokitansky,[2] in 1842, and by Luschka,[3] in 1858. The former did not consider them diverticula, and Luschka spoke of these invaginations into the muscularis and serosal lining as being true glandular formations. Aschoff[4] subsequently studied the pathological anatomy and considered Luschka's description to be that of diverticula that were normally present in small numbers but markedly increased in disease.

Halpert,[5] in a classic study of the morphology of the gall bladder, stated that Luschka had described only aberrant bile ducts in the serosa of the gall bladder near the liver surface. He believed the diverticula should be named "Rokitansky–Aschoff sinuses." Robertson and Ferguson,[1] in their historical review and study of nearly 500 cases, proposed the use of the term "acquired diverticula of the gall bladder" to describe the structures. They postulated four main factors in the development of the diverticula: in-

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creased intracystic pressure; the absence of a muscularis mucosa in the gall-bladder wall; the irregularity of the muscle bundles of the gall bladder; and the independent responses of the muscle bundles to physiologic stimuli.

In 1948, for the first time, March[6] presented cholecystographic evidence of the presence of these diverticula. Since then 24 cases have been reported.[7-28] Three cases in which multiple diverticula were demonstrated radiographically are added below. The pathological findings in 2 patients tend to confirm the thesis that multiple diverticula demonstrated on cholecystographic examination, particularly during the contraction phase, provide evidence of a diseased gall bladder.

Case Reports

Case 1. J. M., a 36-year-old married plumber, was admitted to the Medical Service of the West Haven Veterans Administration Hospital on January 25, 1956, with a 4-year history of episodic abdominal pain, which had begun to occur each day during the 4 months before admission. About 4 weeks after the initial onset of symptoms, he was admitted to the Newington Veterans Administration Hospital for a bout of hematemesis, and a diagnosis of duodenal ulcer was made after roentgenographic examination. After discharge he continued to have nocturnal and postprandial pain, which tended to localize in the right upper quadrant of the abdomen. Four weeks before admission daily episodes of vomiting developed. The pain was aggravated by fried foods, eggs and cabbage. There was no history of chills, fever or radiating pain. A diagnosis of dementia praecox had previously been made.

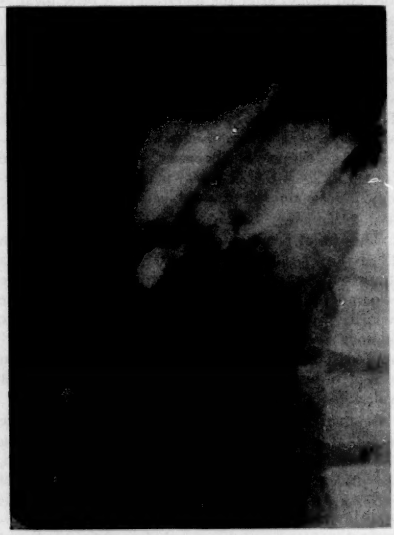

Figure 1. *Preliminary Film of the Gall Bladder in Case 1.*

Physical examination was within normal limits except for the presence of slight tenderness in the right paraumbilical region.

Laboratory tests, including a hemogram, urinalysis, and determinations of cephalin flocculation, thymol turbidity, bromsulfalein retention, serum bilirubin and albumin-globulin ratio, were within normal limits.

A gastrointestinal roentgenologic examination showed no abnormalities. A gall-bladder study on 2 occasions showed good concentration of the dye (Telepaque). A saclike fundus with a proximal constriction and 2d dilatation close to the cystic duct was noted (Fig. 1). After the administration of a fatty meal the gall bladder contracted, and numerous rounded opaque shadows surrounding the body of the gall bladder and seemingly unconnected with it, typical of the presence of diverticula (Fig. 2), were seen. The contraction phase of the study affected mainly the proximally dilated gall-bladder segment, which emptied completely. The fundic portion showed little, if any, decrease in size.

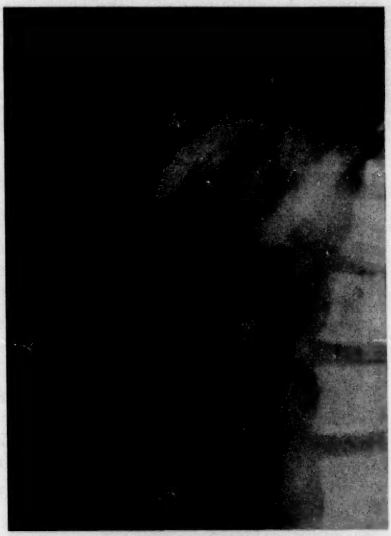

Figure 2. *Film Taken after a Fatty Meal in Case 1.*

A cholecystectomy was performed, and a large, distended, thick-walled, grayish gall bladder was removed. Numerous firm nodules were palpable within the wall. When the specimen was opened many small sinuses containing greenish-black, inspissated material were seen within the thickened wall (Fig. 3). No stones were found. Microscopical examination showed the sinuses to be lined with columnar epithelium continuous with surface epithelium. Many lymphocytes and plasma cells infiltrated the muscle fibers. The diagnosis was chronic cholecystitis and diverticula of the gall bladder.

Case 2. C.R., a 67-year-old engineer, was admitted to the West Haven Veterans Administration Hospital for evaluation of a prostatic nodule, which was found to be due to chronic prostatitis. He had had postprandial abdominal distress, with gas, flatulence, chronic constipation and intolerance to fatty foods for 15 to 20 years and had consciously avoided fatty foods for many years. There was no history of pain localized to the right upper quadrant. Physical and laboratory examinations were within normal limits except for findings consistent with the chronic prostatitis.

X-ray study of the gall bladder revealed a large, well filled organ with a constriction at about the waist. After a fatty meal the proximal portion of the organ contracted better than the other half, and a fine rim of beadlike opacities was noted near the constriction. Cholecystectomy was performed. The gall bladder was dumbbell shaped, with a thickening of the wall at the area of the constriction and small rounded spaces visible in the wall in this region. No stones were found. Microscopical examination showed multiple diverticula, without evidence of inflammation.

CASE 3. L. G., a 39-year-old housewife, was admitted to the New Haven Hospital with a long history of right-upper-quadrant pain and burning, usually postprandial, with radiation to the back and unassociated with nausea or vomiting. Physical examination was within normal limits.

A cholecystogram revealed a dumbbell-shaped, well filled gall bladder with a central constriction. After administration of a fatty meal the proximal portion contracted well, leaving a larger-appearing distal segment with some small, beady radiopacities rimming it.

A cholecystectomy was performed. The mucosa was thickened and smooth, and the wall measured 3 mm. in thickness. No stones were found. The surface showed large areas of shallow thickening that were due to hypertrophy of the muscularis. Microscopical examination disclosed chronic inflammation of the gall-bladder wall.

FIGURE 3. *Surgical Specimen in Case 1.*

DISCUSSION

Anatomic studies of the human gall bladder have demonstrated the presence of diverticula of varying degrees of depth in normal as well as abnormal specimens. These diverticula are lined with normal gall-bladder epithelium. They branch out after invagination into the wall to produce a peculiar gland-like ramification that is a unique process within the gall bladder. This is due to the anatomy of the gall-bladder wall, in which there is no muscularis mucosa. The muscular layer has a counterpart only in the interlaced muscularis of the urinary bladder.[3] The diverticula may be shallow, extending only to the depth of the mucosa itself, or may penetrate into and beyond the muscular coat to the serosal surface. In diseased gall bladders the depth and number of these invaginations is markedly increased. The diverticula generally communicate with the lumen of the gall bladder, but at times the openings may be stenosed, with resultant formation of cystic structures or abscesses. It is also possible that stasis of bile and mucosa within these highly ramified diverticula predispose to calculus formation.

Moore[23] made the observations (also noted in our own cases) of two significant radiographic findings: the presence of an apparent stricture in the region of the gall-bladder neck, causing the organ to appear double, with the portion proximal to the narrowing more contractile in response to a fatty meal; and a rim of beadlike contrast material noted sometimes before and always after the ingestion of a fatty meal.

The constrictions were thought by several authors[6,20] to be congenital and to prevent the ready release of gall-bladder contents on contraction. This was considered to result in increased intracystic pressure, stasis, inflammation and muscle hypertrophy. The total effect was to force the epithelium through relatively weak intermuscular septa, creating diverticula. It is possible, however, that the constriction (noted in 23 of the 27 cases) is a part of the pathologic process and the result of localized muscle hypertrophy.

The rim of beadlike contrast material was seen in 23 of the 27 published cases. Three showed only a thin streak of material seemingly dissociated from the remainder of the contracted gall bladder. In the case reported by Waller and Roberts[28] the radiographic findings consisted of areas of increased density superimposed on the main body of dye that at operation proved to be diverticula in a thickened gall-bladder wall.

Sukman and Daron[13] and Moore[23] emphasize the fact that although an apparently well functioning gall bladder is found on radiographic examination, the presence of multiple diverticula is evidence of gall-bladder disease. This is supported by the fact that in the 23 cases in which operation was performed, evidence of chronic cholecystitis was found in all except 1. Stones were present in 9 cases.

The only exception (Case 2 above) gave no evidence of inflammation on microscopical study, which suggests that the localized muscle hypertrophy may be due to a congenital defect. Assuming that the activity of this muscular ring causes biliary symptoms, they appear to be due to the obstructing mechanism described by March[6] and DeAngelis and Miller.[20] Additional similar cases must be studied before this concept can be fully evaluated.

Pathological studies demonstrate the openings of these diverticula to be usually pin point in size, with racemose dilatations deeper in the wall of the gall bladder. This accounts for the separation of the dye-filled diverticula from the main gall-bladder shadow. While the gall bladder is filled with dye the channels may sometimes be visualized, but when the muscle layer of the organ contracts, the ducts are effectively closed off.

Summary and Conclusions

Three cases are presented showing gall-bladder diverticula on radiographic examination, with localized hypertrophy of the gall-bladder wall with histologic correlation.

The presence of diverticula is considered to be evidence of gall-bladder disorder and, if associated with symptoms, calls for surgical intervention.

The localized concentric hypertrophy of gall-bladder muscle found in these cases is probably of congenital origin.

We are indebted to Drs. Samuel Kushlan, Fred Zaff and Ashley Oughterson for permission to include Case 3 in this report.

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SPECIAL ARTICLE

PASSIVE-ACTIVE IMMUNIZATION IN CERTAIN VIRAL DISEASES THAT PRODUCE PERMANENT IMMUNITY*

Joseph Stokes, Jr., M.D.†

PHILADELPHIA

THE name of Kenneth Blackfan, coupled almost inseparably with that of James L. Gamble, immediately brings to mind what one may call, using an appropriate terminology of astronomy, a galactic event in stellar space implemented by the initiation of full-time clinical chairs at Johns Hopkins Medical School. For in the relative pediatric void then existing in the United States it was as though an active mass of high energy and brilliance that was centered about John Howland, although obtaining more energy from the various elements than from the central figure, had suddenly burst into a number of galaxies, each in its own orbit, furnishing an unusual brilliance of illumination in the darker areas of American pediatrics and, indeed, in all of medicine.

If it were not appropriate at the moment to leave galactic figures and come down to earth, we could well consider what this double galaxy centering in the Harvard Department of Pediatrics had meant to all pediatrics. However, for want of time and to return to a more prosaic framework of reference appropriate to me, I like to think of Dr. Blackfan's starting as a general practitioner in Cambridge, New York, his home town, in a day when men with a consuming scientific bent still had to gain a firm financial footing in practice before embarking on an investigative or academic career, for I happened also to start in general practice before entering academic life and Dr. Blackfan's previous experience and example lent great encouragement and support. Although his major source of energy derived from Baltimore, before this time he was teaching for a short period in Philadelphia with the friendship and support of Dr. Samuel Hamill and of Dr. David Edsall, finally reaching Boston via St. Louis, Baltimore and Cincinnati,

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whereas my own greatest stimulus came directly from Boston before the development of further academic interests in Philadelphia.

Just as the one whom we here greatly honor, Dr. Blackfan, and his associate, Dr. Gamble, merit a long look into recent medical history, so also does the topic I have selected merit similar consideration. For the term passive-active immunization in the major sense used in this discussion appears to be none else than the effort of man to imitate nature in her age-old adaptation of man to certain of his viral parasites, or of these viral parasites to man. Theobald Smith many years ago clearly stated an important maxim, which apparently still holds with increasing significance — namely, that man's parasites so develop that they live with him in adequate symbiosis without permanently destroying him or themselves. Thus, the development of symbiosis is an adaptive process in which apparently both host and parasite participate.

From our own studies in man during epidemics of hepatitis, in which globulin apparently resulted in a permanent type of immunity, and from previous studies in animals by Curley and Gordon with the M.M. virus, and by Fenner with the mouse-pox virus, the following hypothesis was advanced: deliberate exposure of man to certain living viruses by the natural route of infection during the period of immunity conferred by antibody passively transferred, either transplacentally from the mother or by parenteral injection, furnishes a satisfactory imitation of nature's adaptive method in these diseases without evidence of overt infection.

Evidence had been obtained previously by Nicolle and Conseil[1] that convalescent serum given during incubation or just before exposure to measles virus would permit modified but *overt disease* and thus usually would produce permanent protection. The dangers of serum hepatitis (viral hepatitis B) in their method were eliminated later by the use of human immune serum globulin developed by the ethanol fractionation method of Cohn and Oncley[2] and demonstrated in the field by our group in Philadelphia[3] and by Ordman et al.[4] in Boston. This globulin concentrated the antibodies and was far more convenient and stable than convalescent serum. The principle of passive-active immunization was thus further demonstrated.

However, in contrast with the overt disease apparently required in measles for permanent immunity both in the European studies and in the Philadelphia and Boston studies, the work of Fenner[5] in mice (mouse pox) and of our group in man[6] (viral hepatitis A) demonstrated passive immunization with a later superimposed active immunization by the natural route *without* overt disease. In the viral diseases other than measles that we have been studying, the lack of overt disease in passive-active immunization may well have resulted from the tendency of the natural disease under epidemic conditions to be mild or even inapparent in a considerable percentage of cases. On the other hand little is known concerning the possible immunizing effect without overt disease or with very mild disease of repeated exposure to measles virus by the natural route during a prolonged period of passive immunity in newborn infants or in older children, regardless of whether the virus is attenuated. The little that is known comes from the small but interesting group of infants and children in New York City studied by Herrman.[7] These infants were exposed to measles by the questionable method of using nasopharyngeal secretions from patients with active cases during the period of waning transplacental passive immunity and followed in their homes over a sufficient number of years and exposures to measles to suggest that permanent immunity had been produced despite the mildness or absence of overt disease. These studies suggested that the best immunity could be obtained when the infants were exposed at about five months of age — namely, late in the period of waning passive immunity and apparently when clinical symptoms were present after exposure. If these results can be confirmed, they may well suggest that viral diseases can produce permanent immunity even though, as in measles, approximately 98 per cent of the cases in an outbreak are both severe and overt. Thus, such a severe and overt disease may be susceptible to adaptation in man by a method that utilizes the natural circulating immune defenses of the body, together with extremely mild or possibly inapparent disease produced by the natural route of exposure.

With this statement of the hypothesis and brief mention of certain previous studies that form some basis for its favorable consideration, it is important to review certain of our data that led to this suggestion: these data are concerned with three viral diseases, viral hepatitis A (or IH), mumps, and poliomyelitis.

Viral Hepatitis A

Three outbreaks of viral hepatitis A, the first starting in 1948, in which gamma globulin was used for protection, formed the basis for a report entitled "Infectious Hepatitis: The length of protection by immune serum globulin (gamma globulin) during epidemics" in 1951.[6] These outbreaks occurred respectively in an institution for retarded males in New Jersey, an orphanage in Chicago where the disease was endemic and a state training school for boys and girls in Maryland.

In the first institution, housed under the cottage system, gamma globulin was started on August 16, 1948, at the beginning of the first peak in the epidemic, after elimination from the study of Negroes, inmates over forty-six years of age and certain unaffected cottages. In the remaining inmates and cot-

tages the groups were divided by selection of alternate inmates alphabetically in each cottage. Gamma globulin, 0.06 ml. per pound of body weight, was injected intramuscularly into 248 inmates, and 264 remained as controls, the difference in the size of the two groups resulting from the failure of a small number of persons to appear for their injections. In the evaluation of gamma globulin, only cases with jaundice were considered.

In the inoculated group of 248, 5 cases with jaundice (2 per cent) occurred, 4 in the first five days, and 1 on the fourteenth day after injection. During the same period 4 cases of hepatitis without jaundice occurred. No additional cases occurred among the inoculated group, although among the 264 controls, cases with jaundice continued to occur for seven months — 44 cases in all (17 per cent). Since gamma globulin usually does not begin to protect until about five days after its injection, the difference becomes even more striking if the 4 early cases are omitted. If the same five-day period is omitted from the controls, the ratio of comparison of cases then becomes 0.4 per cent in the inoculated group to 15 per cent in the controls. The average duration of jaundice in the inoculated group was fourteen and two-tenths days, and in the control group it was sixteen and two-tenths days. Only 30 per cent of the cases of jaundice occurred in patients under twenty years of age whereas 30 per cent of the total inmates were in the same age group.

With the approval of their guardians and parents, and in view of the mild nature of this epidemic, 50 of the inoculated group together with 4 volunteer prisoners at another institution as controls were tested for immunity to the homologous virus nine months after the epidemic by oral administration of infective serum from the same epidemic to both groups. In 6 of the inmates (12 per cent) mild hepatitis with jaundice and no apparent cases of hepatitis without jaundice occurred after the usual incubation period, whereas in 1 of the volunteers, hepatitis with jaundice and in 3 hepatitis without jaundice occurred.

For various reasons it was not possible to test the resistance of a random sample of the 264 control inmates.

Traces of antibodies remaining after six to eight weeks from the small doses of gamma globulin almost unquestionably would be insufficient to protect against hepatitis. In this outbreak at least 17 cases of hepatitis with jaundice occurred after the sixth week in the control group, whereas none occurred after the sixth week in the injected group, although the contacts in the cottages were intimate. The relative lack of cases with jaundice in the group of 50 younger inmates in the gamma-globulin group whose resistance was tested shortly after the epidemic strongly suggested that the gamma-globulin group, although exposed to the virus during the epidemic, had developed inapparent infection with active immunity superimposed on the passive immunity afforded by the gamma globulin. Though this evidence was suggestive, it was not conclusive.

However, it is difficult to understand why a few cases of jaundice would not have reappeared after six to eight weeks in the injected group, since the degree of exposure from six weeks to three months should have been the same in the injected and control groups and not all the injected group supposedly would have been infected and thereby have developed a passive-active immunity by the sixth or seventh week. Other studies we have carried out in volunteers have eliminated the possibility of active immunization by means of the gamma globulin used (namely, that the active virus of viral hepatitis A was masked in the gamma globulin). Another possible explanation for the failure of reappearance of cases with jaundice after the sixth week should be considered more fully after discussion of the two succeeding examples of passive-active immunization in epidemic hepatitis.

In the second institution, an orphanage where orphan infants were admitted and mothers delivered, and where a small number of graduate nurses trained student nurses for "practical nursing," viral hepatitis with jaundice (not leptospirosis or infectious mononucleosis) had occurred in increasing incidence among new student nurses since 1942.

Late in 1948 we were apprised of the situation, which obviously suggested an endemic focus of infection. At this time (November 7) the inoculation with gamma globulin (0.06 ml. per pound of body weight) of all incoming student nurses was advised and carried out. All these nurses were inoculated within one to one and a half months after the start of their training at the orphanage. On August 29, 1949, the globulin inoculation of incoming student nurses was stopped. The following paragraph indicates the history of hepatitis in the institution before the use of globulin, during the use of globulin and in the nurses admitted to training after August 29, 1949, when the use of globulin was stopped.

During the period January 1, 1946, to November 7, 1948, before the use of globulin, 44 of 139 (32 per cent) new student nurses acquired hepatitis with jaundice. During the use of globulin, when 36 students were admitted in training, 1 case of jaundice occurred, in a student nurse who had received her injection only two days before the onset of hepatitis, thus indicating the virus was still active during this period. Among 20 new students admitted in training after August 29, 1949, there were 6 cases of hepatitis with jaundice and 3 cases of hepatitis without jaundice (45 per cent) before January 1, 1950. Among the 35 student nurses who had previously received gamma globulin and had remained on duty under conditions similar to those obtaining for the nurses admitted after August 29, 1949, 1 contracted hepatitis with jaundice. This nurse was admitted on

March 14, 1949, and was inoculated with globulin on April 23, and jaundice developed on December 20. By chance she did not serve until October 15, 1949, on the fourth floor, where the endemic disease appeared to be most prevalent among the infants and in relation to which the hepatitis among the nurses was most apt to occur. With certain changes in nursing technics carried out in December, 1949, and reported elsewhere, no cases of hepatitis with jaundice have occurred among the nurses.

TABLE 1. *Endemic Hepatitis in a Chicago Orphanage.**

1946 JAN. 1	1948 NOV. 7	1949 SEPT. 1	1950 JAN. 1
139 N.		20 N.	
44 J.		9 H.	
32%		45%	
	36 N.	35 N.	
	1 J.†	1 J.‡	
	3%	3%	

*N = nurse, J = jaundice & H = hepatitis.
†Given gamma globulin 2 days before onset.
‡Not exposed to infective children until fall of 1949.

Table 1 indicates more graphically the progress of the endemic disease and the apparent passive-active immunization of the 36 nurses who received gamma globulin and were then exposed to endemic hepatitis among the infants, 35 of whom later became a test group to be compared with the 20 new nurses admitted after August 29, 1949. Here, again, the fact that cases of jaundice did not reappear in the injected group of 35 nurses two months or more after injection is interesting although less difficult of explanation because the length of exposure of the two groups was different. The injected group in this case was exposed before the controls. That the hepatitis virus A was present among the infants on the fourth and fifth floors was demonstrated by the oral administration to volunteers of stool preparations from 2 infants with chronic symptoms but without jaundice. The incubation period in the volunteers was characteristic of that occurring in epidemic hepatitis.

The third institution studied in 1950 is a relatively well segregated state training school for girls and boys, to which access was obtained at an early stage of a hepatitis epidemic in two cottages, one for girls and one for boys. Leptospirosis and infectious mononucleosis had been eliminated as etiologic factors by the usual serologic tests. The cottages provided all their own food, playrooms and lodging, and thus offered an excellent opportunity for a controlled study. The girls' cottage housed 66, and the boys' 63, all ranging in age from four to fourteen years.

Description of Epidemic and Use of Gamma Globulin

The dose of gamma globulin was reduced to one sixth of that usually given — namely, to 0.01 ml. per pound of body weight. Those to be inoculated were selected alphabetically. That a random selection was attained is indicated by the similar ages, similar dates of admission to the cottages and similar distribution of beds in the sleeping quarters of the groups. All the boys, and all the girls, respectively, remained in intimate contact over the period of ten months of the study except when isolated as a result of hepatitis. Also, 54 adult employees and attendants were given the same dosage of globulin at the request of the administration; 6 employees refused it. These adults lived in separate quarters provided for them on the institution's grounds, and many ate one or more meals a day in the cafeteria of the institution to which the children did not have access.

It is seen from Table 2 that there were 22 cases of hepatitis with jaundice in the 29 boys who served as controls, and 2 cases among the group of 34 receiving gamma globulin. In 1 of these, hepatitis with jaundice developed nine days, and in the other eighteen days, after administration of the globulin. Among the 48 girls who served as controls, there were 20 cases of hepatitis with jaundice, and there were none in the 18 who received gamma globulin. Among the 54 employees who received gamma globulin, 1 case of hepatitis with jaundice occurred seven months later, whereas in the 6 who received no gamma globulin there were 3 cases of hepatitis with jaundice.

A summation of these data indicates that there were 45 cases of hepatitis with jaundice in the 83 controls, and 3 cases among the 106 children and adults receiving gamma globulin.

Here, again, one would have expected a reappearance of jaundice among the injected groups in both boys and girls, particularly in view of the relatively large number of cases occurring in the successive months of December and January. Certainly, at this time even traces of antibody would have disappeared from the circulation, and although passive-active immunization would have been operating during the waning period for plasma antibodies of about two months, it could hardly have been expected to be effective after this time. No simple explanation appears to be available. More recently, in another outbreak in a New Jersey institution, Drake and Ming[8] studied the protective effect of two dosages of gamma globulin with the same lack of reappearance of jaundice in the injected groups, despite the fact that the epidemic continued for fifteen weeks in the control group, whose exposure to the injected groups under the cottage system was more intimate than that of family life.

Such puzzling findings cannot readily be dismissed as possible failure to record cases by attendants, since care was taken that those in charge were not familiar with the differences between the groups. Also, because jaundice was feared such cases were always removed to institutional hospital quarters, and those in charge of the investigations thus had no difficulty

in diagnosis or tabulation. Nor can these findings be dismissed on the basis of bias by individual workers, since three groups of workers experienced in the field of viral hepatitis — one in a different urban center — were following these outbreaks closely. Granted the findings are real, the explanation of their bizarre nature appears to lie in the area of balance between antigen and antibody, in relation either to the absorption mechanism in the intestinal tract or to the fixation of antibody in body cells, possibly in the liver, in the lymphatic system or in the macrophages.

Secondly, the antibodies may remain fixed to lymphoid structures, macrophages or Kupffer cells even though all traces have left the circulation and continue to fix the virus as it enters the host. Such fixation may completely protect the host or permit mild or inapparent infection with immunity without subjecting the host to severe disease with jaundice. Sabin conducted studies on vaccinia, Type B virus of herpes simplex and pseudorabies, all of which suggested that passively transferred protective antibodies may be fixed on certain susceptible

TABLE 2. *Incidence of Hepatitis with Jaundice, Month by Month, in the Inoculated and Control Groups* at the Rosewood State Training School, 1950.*

GROUP	TOTAL NO. IN GROUP	CASES OF HEPATITIS								
		JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	JAN.	FEB.
Boys:										
Control	29	3	5	2	2	1	2	2	5	0
Gamma globulin	34	1†	1‡	0	0	0	0	0	0	0
Girls:										
Control	48	0	4	0	2	0	0	8	3	3
Gamma globulin	18	0	0	0	0	0	0	0	0	0
Employees:										
Control	6	0	0	0	0	1	0	2	0	0
Gamma globulin	54	0	0	0	0	0	0	1	0	0

*Injections carried out on June 12, 1950.
† 9 days after gamma globulin.
‡18 days after gamma globulin.

The following hypothetical considerations should be weighed and studied:

First of all, virus could possibly gain access to the body more readily in the injected than in the control group, since in our studies a larger number of individuals in the injected group are protected after the usual time that the homologous antibodies disappear from the circulation.

The neutralizing antibodies in the circulation against viral hepatitis may be present in the secretions of the intestinal tract, coating the virus and thus protecting a larger amount of virus from destruction in the upper bowel than in the controls. This could result in earlier, inapparent infection of the injected group than of the control group, perhaps through the lower bowel.

Virus coated with neutralizing antibody may well be picked up more readily by the lymphoid tissues in or around the intestinal tract than in the controls and thus gain access to the body earlier than in the controls, again to produce inapparent infection because of the presence of circulating antibody.

These hypothetical mechanisms could operate whether a single viral body or a large number of viral bodies were necessary for infection.

host cells and thus may furnish protection well after the time that the circulating antibodies disappear.

These diseases obviously differed in their point of attack. For example, pseudorabies could be prevented by a relatively small amount of intranasal immune serum in the guinea pig when inoculation occurred by this natural route.

Thirdly, it is also conceivable that some other disease prevalent in the controls and from which the injected group had been protected by the globulin had left the control group more susceptible to hepatitis. This seems unlikely because we are aware of no disease that occurred in the controls.

There is still much to be learned concerning the exact method of formation of antibodies. When this method is more fully understood the solution of the present problem will unquestionably be greatly aided. For instance, an interesting theory of antibody has been proposed by Jerne[9] postulating the spontaneous presence in the blood of an animal of small numbers of antibody molecules against all antigens to which the animal can respond, and delegating to the antigen the sole role of carrying such specific globulin molecules from the circulation into the cells in which these molecules can induce the production of more

of their kind. This theory might explain how passively transferred protective antibodies are fixed in the macrophages, plasma cells or lymphocytes.

Since I believe that the phenomenon of passive-active immunization as we have studied it, however puzzling, is a real one, and because the second hypothesis — namely, fixation of antibody to susceptible cells — appears more tenable, it seems appropriate to approach this problem through studies on antibody as related to mouse pox, along the lines of Fenner's studies in this disease or through poliomyelitis, Type 2, in rodents. Certainly, the solution of the problem

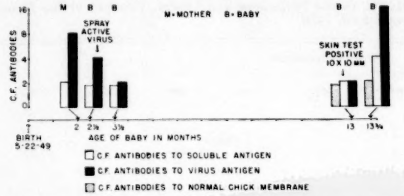

FIGURE 1. *Passive-Active Immunization of an Infant against Mumps.*

can be aided by means of studies in man, and it is to further studies in this more entertaining "rodent" that I should now like to turn.

MUMPS

A single case is scientifically almost valueless but is always a joy to the clinician, but when that one case is a grandson, it becomes a magnificent obsession. His story is best told from Figure 1, which indicates his mother's anti-V* and anti-S antibodies, the time during his waning passive immunization at which he was sprayed in the nose and mouth with active mumps virus and the subsequent alterations in his antibody picture. That there is evidence of an active immunization superimposed on a passive immunity seems highly probable, in view of the positive skin test and the rise of anti-V antibodies after the skin test, which is so typical of an anamnestic response. He has been exposed to mumps at least once since that time without contracting the disease but, as you are well aware, about 40 per cent of mumps is inapparent and having weathered both grandmothers once, I have lacked the temerity to suggest a continuing serologic study. We have not had the time to pursue further this evidence for whatever it may be worth, but have had plans to do so since this approach appears to be basically a sound one.

POLIOMYELITIS

The final studies I should like to mention quite briefly are those, still in their earlier stage, deriving their major impetus from Dr. Hilary Koprowski, who with Jervis and Norton began investigations about six years ago concerning active immunization against poliomyelitis with viruses Types 1 and 2 attenuated by serial passages in rodents and inoculated orally.

Neutralizing antibodies to both attenuated strains SM and TN have been produced at highly satisfactory levels and have continued with insignificant variations in amount over five or six years. This warrants the belief that they may remain elevated for a considerable time and perhaps permanently.

From the beginning of Dr. Koprowski's studies it has been our belief that there would be difficulty in the wide-scale use of living virus strains unless passive-active immunization were used rather than active immunization alone. Apparently, antibodies at relatively low levels in the circulation will not limit in any way the production of an active immunity from orally administered living virus. We therefore proposed to Dr. Koprowski, first, that the attenuated strains of Type 1 and Type 2 virus, SM and TN respectively, be administered orally to children at the same time as immune serum globulin, tested for antibodies, was inoculated intramuscularly in amounts somewhat larger than those Dr. Hammon and our group had used in 1951 and 1952; and, secondly, that a study be initiated with the Type 1 SM strain in newborn and slightly older infants possessing Type 1 antibodies from their mothers. Together with Drs. Koprowski, Jervis and Norton, of Pearl River, and Drs. Hunt, Jr., Hummeler and myself, of the Philadelphia group, and also with Dr. Flack, of Clinton Farms, we have progressed far enough in this investigation to know that the large group of older children studied develop antibodies and become infected in the same manner as children without the globulin injections[10] and that the infants we have studied at two or three months could be infected without symptoms and with striking increases of homotypic antibodies.[11] In such infants infection occurred with the presence of large amounts of attenuated Type 1 SM virus in the stools over several weeks without any symptoms and with entirely adequate weight gains when compared with control infants in the same nursery. Actually, if the population as a whole becomes immune to all three types of poliomyelitis virus, it apparently would not matter whether one used a highly attenuated strain or a somewhat more virulent strain; in fact the latter might be the more important in such passive-active immunization.

It has not been my intention to present more than a brief outline of our approach to the problem of poliomyelitis, and yet it is our belief that the present dead vaccine now in use is a sufficiently inadequate answer to our problems in this field so that any hopeful approach toward permanent immunity is worthy

*These determinations were carried out by Dr. Michael Sigel at the Virus Diagnostic Laboratory, Children's Hospital of Philadelphia.

of comment, even though the studies may figuratively and literally still be in their infancy.

Conclusions

For our present purposes, then, these studies are all the more important since they further explore the imitation of nature's adaptive method — the deliberate exposure of man to his viral parasites by the natural route during the period of passive immunity conferred either parenterally or transplacentally.

Active-passive rather than passive-active immunity may well be studied, but in such a method injections would be needed — first the antigen and second the antibody. It seems preferable to test thoroughly the capabilities of the newborn infant through inoculation by the oral route in certain viral diseases and possibly by the respiratory route in others. Assurance of antibodies from the mother could be obtained by her direct active immunization, if necessary.

The present studies are but a beginning. We hope to explore these problems further as the opportunity arises.

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MEDICAL PROGRESS

HEALTH IN COLLEGES AND UNIVERSITIES

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THE health of students, faculty and staff of colleges and universities is gradually becoming a source of official concern to the governing authorities of institutions for higher education. The concept is slowly gaining acceptance that some provision should be made by the college or university for the promotion and maintenance of health and for the treatment of illness or injury whenever they occur. Community resources, however excellent they may be, do not meet the needs of college personnel without a local organization or service designed to bring the student or staff member and the physician and his professional resources together in such a way as to be mutually advantageous and with a minimum loss of time. This review, supplementing one published in 1953, will emphasize the health problems and organizations of large colleges and universities, although it is apparent that the health needs in the small colleges are very similar, even if the methods of meeting them require much modification.

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Fourth National Conference on Health in Colleges

The most important event concerning the promotion of health in colleges that has occurred since the last report was the Fourth National Conference on Health in Colleges, held in New York City, May 5 to 8, 1954. This conference, the fourth of its kind since 1931, was sponsored by 46 national health organizations, with the National Tuberculosis Association and the American College Health Association taking the initiative in the preliminary planning and the follow-up activities. In attendance at the meeting were 527 delegates from all parts of the United States and Canada, together with a few representatives of other nations. Indicative of the widespread character of interest was the fact that among those attending the meeting were 18 college presidents, 38 deans, many faculty members interested in counseling problems, physical educators, nurses and health educators. A few students were invited, and their participation and presence were so helpful and welcome that strong sentiment was expressed by many delegates that more of them should be present at the next conference of this type.

Aside from a general session devoted to a discussion of college-health problems by a panel of six college presidents, the conference was a "working conference," being divided into 16 different sections, each considering for several days one particular aspect of health promotion. The summary of all the various deliberations has been published by the American College Health Association.[1] This volume discusses in varying degrees almost all the acute and chronic problems facing college-health workers and administrators and should serve as a major source book for all who are interested in college health for the next five to seven years, or until a fifth conference on health in colleges is held and its proceedings published.

Another volume of prime interest to college-health workers was derived from a conference on the college and student health by Ethel L. Ginsburg.[2] The author quite properly points out that although accomplishments up to this time are commendable, the fact remains that two thirds of the colleges take little or no responsibility for the health of their students. The individual student may enroll at a college where practically all his health needs can be met and active programs designed to keep him well are in effect. Statistically speaking, it is more likely that he will find himself in a college that lets him take his chances on health. "Responsibility is the point at issue," as she views the college-health situation.

In her discussion, Ginsburg further considers the colleges' responsibility for student health, the characteristics and scope of a good college-health program and the various devices or methods by which responsibility may be translated into action. This volume supplements and does not duplicate the *Conference Proceedings.*

As a result of mental-health programs in various colleges in the United States and various other countries, Mexico and Costa Rica among them, the World Federation for Mental Health and the International Association of Universities sponsored an international conference on student mental health at Princeton, New Jersey, from September 5 to 15, 1956. About 36 persons participated in the conference, nearly half of whom were delegates from overseas. In addition to college psychiatrists, college deans, psychologists, counselors, cultural anthropologists, religious counselors, administrators and students were represented. The delegates were selected because of their experience or special interest in this field. Before the conference an annotated bibliography of the literature on college students and their psychologic characteristics and mental health was compiled and published.[3] A volume on college mental health derived from the conference discussions is being prepared, together with another volume made up of papers submitted by the delegates before the conference.[4] It is hoped by the sponsors and planners of the conference that the deliberations of this group will serve as a basis for the development of college and university mental-health programs in various countries throughout the world, and also that an open conference of considerably greater size may be held in a few years that will serve to facilitate developments in this field.

As part of the preliminary planning for the Fourth National Conference on Health in Colleges, an attempt was made by the conference president, J. L. Morrill, president of the University of Minnesota, to learn what the principal health problems appeared to be from the standpoint of the college president. He wrote to 200 of his colleagues who were heads of colleges or universities, and received significant replies from 116 of them. He asked them what the outstanding administrative problems were in their own institutions and what, in their opinion, were the major health problems of their students. Financing an adequate health program and obtaining well qualified physicians, two related problems, were the ones most often mentioned in the administrative category. Nearly half the presidents were concerned about the co-ordination of student counseling programs. More than half the presidents reporting (68 of the 116) said that the major health problems in their institutions concerned the emotional difficulties of their students. Poor health habits, with much reference to diet, sleep and rest, constituted the second largest category (46 out of 116).[5]

As another part of the preliminary preparation for the Conference, Moore and Summerskill,[6] of Cornell University, through a grant from the Continental Casualty Company and under the auspices of the American College Health Association, made a careful survey of health-service facilities and personnel in colleges and universities of the United States as they existed in 1953. At that time there were 1887 colleges in the country; 1545 were interested enough to answer inquiries about the survey, 1057 directors of health services were interviewed, and 768 health services were found that had a clinical program consisting of more than routine first aid. Of this group of 768 colleges more than half attempt to care only for minor illnesses or injuries, and of the remaining 311 that care for major medical illnesses, only 65 have facilities for surgery.

The quality of health care that a student may receive when he goes to college thus varies almost indefinitely. Only about 20 per cent of colleges have a fully developed health program, but, of course, this percentage includes most of the larger universities. This suggests that a part of the investigation of a prospective college should include some checking on the quality of the health service by the student or his parents.

As a general rule, most colleges with a good health service have from 5 to 7 visits each year by each student, this figure tending to be larger in the small college away from a large city than in the urban university. A recent tabulation at Cornell University

indicates that before students leave the University, 95 per cent require medical care and 42 per cent require hospitalization.

Moore and Summerskill found that the percentage of colleges with comprehensive clinical programs does not vary much from one region of the country to another, nor with respect to the location of the institution in a rural area, in a small city or in a large city. It was their impression that the institutions that set the highest standards of medical care for students were those with the highest academic standards. Medical histories, x-ray studies of the chest and vision examinations were required at approximately half the colleges surveyed. Dental examinations and psychologic adjustment tests are required in about a third. About 400 colleges require smallpox vaccinations for entering students, but more than 700 do not. Only about 1 college in 10 requires that students be immunized for tetanus and typhoid. About half the health services assume some responsibility for standards of sanitation in campus lodgings, dining rooms, washrooms and similar places. Physicians direct 42 per cent of the college health services, and of this number half are employed full time. Nurses direct 1 out of 4 health services. About 200 colleges have a full-time physician, about 500 have a part-time physician, and more than 400 have no staff physician at all. Health-service staffs are more likely to include full-time nurses than full-time doctors. If a college has a health service, the chances are 9 out of 10 that students entering that college are required to have a physical examination. Whether such an examination is conducted by the student's own physician or by the college depends on the individual college; there is a 50-50 split on this procedure. Health-education courses are offered at 80 per cent of colleges with a health service and are required at half these colleges. Academic credit is granted for this work in nearly every institution. The college health service is nearly always responsible for the medical care of athletes.

A third of the health services operate on less than $5 per student per year, a third operate on $5 to $10 per student per year, and a third operate on more than $10 per student per year. In general it can be said that the average spent on student health throughout the country is approximately 20 per cent of what it would cost to maintain a fully satisfactory health service.

A number of new textbooks on college health have been published recently, two notable ones being by Schifferes[7] and Johns, Sutton and Webster.[8] Both are thoroughly in keeping with recent advances in health education as well as health services.

Who Should Perform the Entrance Physical Examination?

Interest in effecting more economy in the maintenance of college-health programs is evidenced by a current debate in progress among health-service directors over whether it is more desirable to have the entrance physical examination and health evaluation done by the college health service or by the family physician. This question is of great importance, not only from the standpoint of costs but also because the amount of effort, ingenuity of organization, paper work and possibilities for confusion in examining an entering class of 2000 to 5000 students is formidable indeed.

Those who favor having the examination done by the family physician or some other private physician point to the savings in money to the college, the elimination of a very strenuous period in the early part of the first semester during which the examinations were formerly performed and more time on the part of the staff for special consultations and necessary aptitude or other psychologic tests. Some persons do not like the station-to-station type of physical examination in vogue in many of the larger universities. Dyke,[9] of the University of Illinois, has reported favorably on the system of examinations by the family physician. He believes that most of the records that he receives give evidence of careful evaluation and that misrepresentation of physical defects is minimal. The University of Michigan is also changing from the college type to the family-physician type of examination.

Those who advocate the health evaluation after the student comes to college point to the advantages of the uniformity of the examination and the recommendations made, the desirability of having the records such as to be quite familiar to the health-service physician, and the need of having an intimate knowledge of which particular students can do physical education and athletics, a decision that the family physician would not be in as good a position as the college physician to make. The family physician may at times hesitate to mention some of the things that he thinks might keep the student out of college, such as fainting episodes, convulsive seizures, arrested tuberculosis and emotional disorders. Advocates of this system point out that the first exposure of the student to his health service can be an educational experience of considerable value and that the doctors may be able to give good health counseling at this time. No physical examination is of much value if there is no follow-up study and the person who does the examination is not familiar with the local medical profession he may recommend for subsequent consultations.[10]

Financing the Health Program

At the Fourth National Conference on Health in Colleges a special committee considered the problems involved in financing student-health programs. This was also one of the chief problems that concerned college presidents in the survey referred to above.

This committee suggested that no one plan of payment was suitable to all colleges. Among the possible prepayment plans are purchase of commercial insurance, self insurance, Blue Cross or Blue Shield plans, and contracts for service usually associated with some type of group practice. Various combinations of these plans are in effect in different colleges. Stanford University is the outstanding example of medical service furnished by a group in practice, one member of the group being designated as the director of the student-health service.

Self-insurance plans have gained very little acceptance up to this time. Blue Cross and Blue Shield organizations have failed to make much headway, because the officials of these organizations have not as yet realized the full opportunities to be gained from devising special plans suitable to student needs. The commercial insurance companies have made strong efforts to capture this field and have made considerable progress.

The plan now in operation at Harvard University is representative of several of the devices used by universities and some of the larger colleges. This plan is intended to act as a supplement to a fully organized student-health program. Each student pays a regular health fee, and, in addition, he may purchase insurance, which in the Harvard plan costs $14 per academic year or $19 for a full calendar year. This entitles him to payment for nearly all medical, surgical or psychiatric attention that he may need up to $1,500 for each illness or injury. The limitations in this plan are as follows: not over $19 a day for hospital accommodations; not over $250 for laboratory and x-ray charges; and no allowance for elective conditions or for illnesses present at the time that the insurance is taken out. No allowance is made for refractions, routine dental services other than injuries to sound natural teeth or for injuries or illnesses incurred during service in the armed forces. This plan has been in effect at Harvard for more than a year, and the first year's experience was so favorable that benefits were substantially improved, the over-all limit during the first year being $1,000 for each illness or injury (now $1,500).

It is to be hoped that such plans can be utilized by every college student as soon as possible. The Harvard plan is not required of students who make appropriate application for exemption from such insurance. Those who do not take it are assumed to have adequate coverage of another kind or are financially independent; hence, the University does not assume any responsibility for hospital or medical expenses in the event that they become ill. During the first year of operation 97 per cent of all students in Harvard College and 90 per cent of all students in the University were covered by this insurance plan. The first expensive and serious illnesses incurred in students who applied for and obtained exemption have been instrumental in developing an increasing student acceptance of the plan.

Internal Medicine

A good internal-medicine service is the foundation and main strength of any health program, and this is just as true in colleges as elsewhere. Under ordinary circumstances the college experience is so much like that of the general population that it does not draw as much attention as some of the surgical and psychiatric problems. The most common of the serious disorders that affect college students are infectious mononucleosis, infectious hepatitis and viral pneumonia. At Harvard University, with a student population of about 10,300, 76 cases of mononucleosis, 43 cases of infectious hepatitis and 11 cases of viral pneumonia were diagnosed in the academic year 1954-55. Two new cases of pulmonary tuberculosis were discovered, and 32 persons with inactive lesions were under supervision. The large number of cases of hepatitis was unusual; there were 23 cases in 1953-54 and 12 in 1955-56.

A valuable service to students and faculty members is that of carrying out various immunization procedures. Those about to go abroad particularly appreciate this care, not only getting the various inoculations but also learning what ones are necessary for the countries they plan to visit. Indirect health education, such as the preparation and distribution of brochures on common disorders affecting students, is a primary function of the medical service. "Every contact a teaching opportunity" should be a fundamental premise in any student-health service.

Tuberculosis Control

The Committee on Tuberculosis of the American College Health Association has recently called attention to the need for continued alertness to the presence of tuberculosis in college students, even though the pharmacologic treatment of this disease has advanced greatly during the last decade. Cases are still being diagnosed in all colleges; in spite of the fact that the diminishing trend of the last few decades continues, the time is not yet at hand for relaxing diagnostic and control measures. During the academic year 1952-53, 564 colleges carried on active case-finding programs. Unfortunately, the number of new cases found is not known, but if past experience is to be relied upon, it should be about 500 cases.

Although experience in the United States has been very encouraging in the control of tuberculosis, this disease remains one of the chief hazards to student health in most European countries as well as those on other continents. This is reflected in an increased concern on the part of student-health directors about the relatively high rate of tuberculosis in foreign students wishing to study in this country.

Surgical Aspects of a College-Health Program

The method of handling surgical procedures in the student body is of great concern to parents as well as to the students themselves. Public relations of the college are often acutely affected by the degree of efficiency with which surgical emergencies are met. Whether the institution is large or small, located in a city or in a rural area, it should be its direct responsibility to see that proper surgical care is available when it is needed. More frequently than in other age groups, the college population is involved in accidents. In his carefree exuberance, the college student is likely to forget the restraints and caution of the more mature person. The college girl or boy is in the process of gaining maturity in judgment at the college age. Rules and regulations are looked upon as things he has had to abide by at school, but at college this should be different. There is no question that the group from eighteen to twenty-five years of age is considered the most accident prone, as shown in states where compulsory automobile liability insurance is law. Much of the surgery to be provided must therefore be considered to consist of the surgery of trauma and its sequelae. In addition, the surgical infections, although not all serious, loom large in any diagnosis table submitted by a college-health service.

In the most complete study published[11] on accidents to college students, the American College Health Association and the National Safety Council have reported on some 13,300 accidents, both on-campus and off-campus, covering 11 institutions in the first year and 9 in the second. This report, although of interest to a limited number of medical and college administrative offices, was incomplete. Among the interesting findings, however, are the following:

No deaths were reported.

On-campus accidents occurred most frequently in athletics, in laboratories, in dormitories and on the sidewalk. (Athletics account for 50 per cent.)

In the intramural sports program, football and basketball accounted for 70 per cent of the injuries.

Sixty per cent of the accidents occurred on the campus.

About 75 per cent of all accidents occurred between noon and midnight.

About 8 per cent required hospitalization.

Accident severity rises from 8 p.m. and continues at a high level until 4 a.m.

Table 1. *Types of Injuries.*

Injury	No. of Injuries					Totals
	1932-1937	1937-1942	1942-1947	1947-1952	1952-1954	
Sprains	636	426	210	344	86	1702
Strains	363	287	96	145	53	944
Joint contusions	219	73	87	52	17	448
Muscle contusions	526	350	111	60	18	1065
Simple contusions	281	93	103	97	22	596
Fractures & dislocations	223	232	105	181	47	788
Lacerations & abrasions	264	89	25	40	6	424
Inflammations & infections	300	131	66	48	9	554
Internal injuries	102	81	39	115	26	363
Miscellaneous	243	152	67	42	6	510
Totals	3157	1914	909*	1124	290	7394

*From fall, 1943, until spring, 1946, University on war basis, with organized sports continued only informally & on limited scale.[11]

Regulations for Participation in Athletics

Since half this on-campus injury rate is attributed to the athletic program and two sports in the intramural program show a high rate of accidents, it behooves those responsible to find out why. All sports programs involving body contact require certain rules and regulations by the student-health department. All participants in sports involving an individual physical effort beyond that of tennis or golf should undergo a complete physical examination once a year, and any student who has experienced a serious illness or major surgical procedure should be re-examined before being authorized to participate in strenuous sport.

Such examinations should be sufficiently detailed to rule out impairment of function in the cardiovascular, respiratory, excretory and central nervous systems. Furthermore, in body-contact sports it is essential that visual acuity be high — in other words, all participants with seriously restricted or absent vision in one eye should be excluded from competition. In cases in which one of the bilateral organs has been surgically removed or is congenitally absent (kidney, testes), the rugged body-contact sports should be denied; when extensive surgical scars are present (extensive burns, splenectomy, laparotomy and so forth), the student should be advised to seek some other form of physical exercise or other noncontact sport. Participants who show broken or absent teeth and are wearing some form of dental prosthesis require protection by some special form of alveolar splint during body-contact competition. At

the present time, an ever-increasing number of students admitted to college show more and more such physical limitations — approximately 20 per cent of the freshmen at Harvard exhibit visual impairment of 20/200 or less in one eye or both. Such, then, are the more common physical defects that the college youths of today exhibit and for which restrictions by the health service must be enforced, if the frequency of on-campus injury and accident is to be reduced. It is essential that every school or college have a written code of rules and regulations, known to participants, parents and the school or college authorities,[12] defining the responsibilities for sports injuries.

Treatment of Injuries Sustained in Athletics

In addition to any required physical examination to provide for the limitation of participants in body-contact and other sports, the health service must provide for adequate medical coverage of injuries sustained in scheduled practice or game sessions. The early application of approved methods of treatment to these injuries is essential. As much as an hour's delay in the application of therapeutic measures can prolong the recovery time beyond reason. The sport season is short. Every day of participation is important to the player and to his coach. Every minor sprain may be aggravated by continued play; every potentially serious injury needs medical supervision on the field. Although 13 per cent of all sports injuries in organized athletics are serious,[13] no one can forecast which one may be anticipated. In other words, a qualified team physician must be present at the practice or game whenever body contact is involved.

Intramural Athletics

Perhaps the most difficult college-sports program to administer from the point of view of the athletic and health-service departments is that pertaining to intramural athletics. The authority to appoint doctors to athletic teams must of necessity remain with the college-health service. That it is a good program nobody can deny; that it should be voluntary and played for fun is desirable. Restrictions of any kind are abhorred by the volunteer participants; yet the health service is certainly involved in its interest in the prevention and treatment of injury. There should be a minimum of regulation, but there must be some supervision when body-contact sports are concerned. It would be utterly foolhardy to allow a participant to report for the first time in the final game of the championship series without any practice or any serious physical conditioning. It is reasonable to expect those accepted for play to participate in practice or game at least three times a week during the scheduled season. Not only must a team know the rules of the game, but also individuals must learn team play to help one another and obtain a co-ordinated offense or defense in the intramural as well as in varsity competition. There is no question that a well rounded offense and defense where the individuals work together coherently has a favorable influence on the frequency of injury. Particularly is this true for the sports of football and basketball. Therefore, it is reasonable to place a few health regulations on any intramural program and to provide for the proper medical attendance at practice and game sessions.

TABLE 2. *Parts of the Body Injured.*

REGION	NO. OF INJURIES				TOTALS
	1932-1937	1937-1942	1942-1947	1947-1954*	
Abdomen	18	10	1	8	37
Achilles tendon	31	5	3	4	43
Ankles	*344*	*200*	*125*	*226*	*895*
Arms	38	35	12	15	100
Back	87	57	5	32	181
Buttocks	29	10	0	3	42
Calves	147	91	48	14	300
Chest	75	48	55	35	213
Crotch	27	0	0	1	28
Elbows	53	38	21	12	124
Face	*228*	*122*	*44*	*48*	*442*
Feet	187	68	39	45	339
Groins	114	108	39	21	282
Hands	*288*	*109*	*55*	*41*	*493*
Head	*182*	*109*	*71*	*140*	*502*
Heels	32	8	2	3	45
Hips	58	26	0	4	88
Knees	*426*	*301*	*137*	*273*	*1137*
Iliac crest	30	29	24	28	111
Neck	20	14	1	11	46
Shin	54	16	7	60	137
Shoulders	*212*	*189*	*64*	*129*	*594*
Teeth	14	1	0	11	26
Thighs	*416*	*240*	*113*	*142*	*911*
Throat	11	6	6	15	38
Viscera	35	42	16	12	105
Wrists	51	32	21	31	135
Totals	3207	1914	909	1364	7394

*Last period for 7 academic yr. rather than 5.[10]

Types and Locations of Injuries in Sports

To illustrate twenty-two years of experience, Tables 1 and 2 record the types of lesions and their location by parts of the body.

(*To be concluded*)

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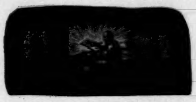
MEDICAL INTELLIGENCE



COBALT-INDUCED MYXEDEMA*

Report of a Case

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COBALT is a component of the vitamin B_{12} molecule and as such is essential to erythropoiesis. Thus far no clinical evidence of cobalt deficiency has been demonstrated in man. However, when cobalt is administered to man and animals in amounts far greater than the estimated daily requirement an absolute polycythemia, with hyperplasia of the bone marrow and reticulocytosis, results.[1,2] More recently cobalt has been reported to elicit favorable responses when vitamin B_{12} fails in anemias of diverse etiologies: those associated with chronic infection,[3,4] chronic renal disease,[5] prematurity,[6] pregnancy[7] and sickle-cell disease.[8] In the past three years a proprietary preparation containing cobaltous chloride and ferrous sulfate has been used extensively in pediatrics, especially in the treatment of iron-deficiency anemia[9] and the anemia of prematurity.

In addition to the favorable results mentioned above, numerous reports of cobalt toxicity and undesirable side effects have appeared. These have included rashes, anorexia, nausea, vomiting, tinnitus and nerve deafness. Concerning children particularly, recent reports of significant interference with thyroid function have appeared.[9-15]

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To illustrate the potential danger of the indiscriminate use of such preparations containing cobalt as well as iron in the routine treatment of anemias, the following case is considered worthy of presentation.

CASE REPORT

D. H. (M. G. H. 867386), a 17-month-old girl, was referred to the Children's Medical Service by Dr. Robert D. Cox with the chief complaint of an enlarged thyroid gland. She had been perfectly well until approximately 3 months previously, when coryza, a slight rise in temperature and a cough developed. Because the upper respiratory infection and fatigue persisted she was taken to the family physician, Dr. Henry R. Lareau, who noted a hemoglobin of 9 gm. per 100 ml. and prescribed a liquid preparation containing ferrous sulfate and cobaltous chloride. She was given 0.6 ml. per day of the preparation containing 40 mg. of cobaltous chloride, or 4 mg. per kilogram of body weight. In about 2 weeks she was apparently well again, her respiratory infection having cleared and her activity increased. The medication was continued, nevertheless. During the next 6 weeks she remained generally well, although it was noted that the feet were colder than normal and the stools somewhat harder. One month before admission her mother first noted a lump in her neck, and during the next week the child became less active and her appetite decreased. Two weeks before admission the hemoglobin had increased to 11 gm. per 100 ml. but an obvious, large goiter had developed. In the next week and a half she became very listless and refused to walk; her appetite decreased further, and she seemed to have difficulty in swallowing, taking only liquids. A weight loss of 1.1 kg. (2½ pounds) was noted. The iron-and-cobalt preparation was given up to the day of admission, for a total of 12 weeks.

Physical examination showed a well developed and well nourished, quiet, pale girl with little affect, who lay in bed and refused to sit or stand. The skin was soft, smooth and moist, but the lower extremities were cold. The thyroid gland was diffusely enlarged to approximately 4 times the normal size, the right lobe being larger than the left (Fig. 1). It was stony hard, smooth and nontender and was not fixed to the skin or underlying tissues. A bruit could be heard over the lateral lobes. The lungs were clear. The heart did not appear enlarged to percussion, and no murmurs were heard. A smooth, firm liver edge was felt 1 cm. beneath the right costal margin; the spleen could not be felt. There was no remarkable lymphadenopathy, the deep tendon reflexes were normally active, and the remainder of the examination was within normal limits.

The temperature was 99°F., the pulse 80, and the respirations 20. The blood pressure was 90/50.

The hemoglobin was 11.5 gm. per 100 ml., and the white-cell count 9500; urinalysis was within normal limits. X-ray study revealed generalized enlargement of the heart (Fig. 2), with no esophageal obstruction on barium swallow. Wrist films showed the bone age to be consistent with the chronologic age. An electrocardiogram showed low-voltage QRS complexes and ST-segment depression. The serum was gross-

ly lipemic; the cholesterol was 694 mg. per 100 ml., and the carotene level 1.3 units per milliliter. The protein-bound iodine of serum drawn during the morning after admission was 0.7 microgm. per 100 ml., and the 24-hour uptake of radioactive iodine (5 millicuries given 48 hours after discontinuance of cobalt) was 69 per cent.

The preparation containing iron and cobalt was discontinued immediately on admission. During the 1st few hospital days the child continued apathetic, inactive and anorectic. Initially, she took only liquids and seemed to have difficulty in swallowing despite absence of x-ray evidence of obstruction. At no time was respiratory distress noted.

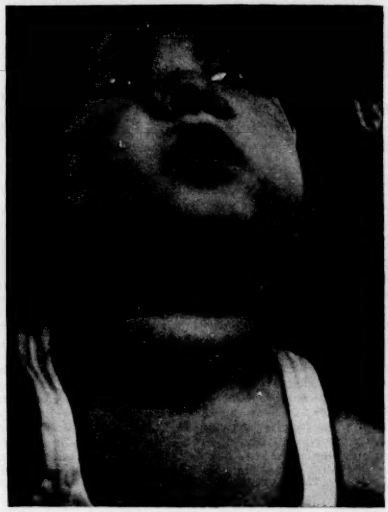

FIGURE 1. *Appearance of the Goiter on Admission.*

The low-potential electrocardiogram and the cardiac enlargement were considered consistent with myxedema heart, although on admission no sign of decompensation was present. The child was followed closely for evidence of cardiac tamponade, but no pulsus paradoxus was noted. On the 3d hospital day, when evidence of congestive heart failure appeared, the liver edge had moved down from a normal level to 4 cm. below the costal margin, and the neck veins were full and pulsating. The vital signs remained constant, and the chest clear.

Because of the potentially dangerous cardiac condition, regarded as secondary to the thyroid insufficiency, 30 mg. of *U.S.P.* thyroid per day (75 mg. per square meter of body-surface area per day) was started on the 4th hospital day. This dose was calculated to give adequate substitution therapy without causing suppression of TSH secretion by the pituitary gland. By the 7th day the liver edge had receded to the costal margin, and there was no longer any suggestion of failure; the thyroid gland had become somewhat softer and questionably smaller. Meanwhile, the child had become more active and communicative, taking an active interest in her environment, and had begun to eat well. By the 10th day, although a chest film showed no change in cardiac size, the serum cholesterol had fallen to 336 mg. per 100 ml., and the electrocardiogram showed increased voltage, which now appeared to be within normal limits. She was discharged on the 15th hospital day, to continue the same dosage of thyroid at home; the thyroid gland was definitely softer and slightly smaller.

During the next 2 weeks the gland decreased further in size. The child continued alert, bright and active, with a good appetite.

At follow-up study approximately 1 month after admission and 25 days after thyroid was started, the left lobe of the gland (which had always been smaller) was no longer palpable, whereas the right lobe and isthmus were still palpable, slightly enlarged and firm. On visual inspection, however, the gland was not discernible. The serum cholesterol had continued to fall to 257 mg. per 100 ml., the chest film revealed definite decrease in heart size, and the electrocardiogram showed further increased voltage. Thyroid was now omitted.

Follow-up study approximately 2 months later showed the thyroid gland to have completely resolved and to be no longer palpable. The serum cholesterol was 173 mg. per 100 ml., a chest film revealed normal heart size, the serum protein-bound iodine was 7.0 microgm. per 100 ml., and the radioactive-iodine uptake at 24 hours (5 millicuries given) was 23 per cent.

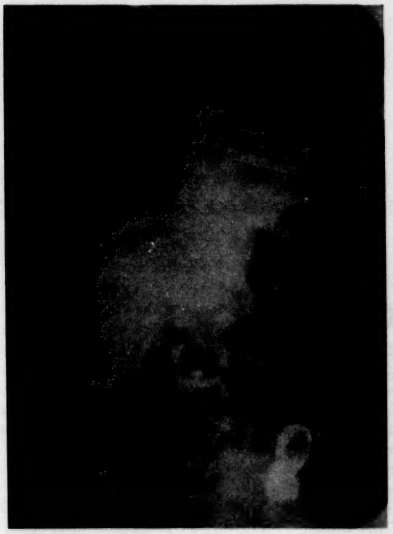

FIGURE 2. *Roentgenogram of the Chest, Showing Cardiac Enlargement.*

DISCUSSION

The role of cobalt in hematopoiesis has been reviewed in an excellent paper by Bush.[10] The goitrogenic effect of cobalt was first suggested by Kriss et al.,[11,12] who noted this incidentally while treating 4 children and 1 adult with sickle-cell anemia. After a period of treatment as short as six to nine weeks a goiter was noted with the laboratory evidence of a depressed I^{131} uptake. Subsequently, in 1 case, after three months of treatment, obvious clinical myxedema appeared, with a protein-bound iodine of 1 microgm. per 100 ml. These patients were being given cobalt in a daily dosage of 3 or 4 mg. per kilogram of body weight. Within a month after withdrawal of cobalt

the children were clinically euthyroid, and the goiters had undergone almost complete resolution without other specific treatment. In 1 case resumption of cobalt administration was followed by a marked fall in I^{131} uptake, with a characteristic rise to higher than normal levels on cobalt withdrawal.

Subsequently, Klinck[13] reported 10 cases of goiters in presumably euthyroid children that he had examined pathologically. In these cases a constant feature was diffuse and uniform thyroid enlargement, showing microscopically a remarkable degree of hyperplasia. There was no evidence of malignant change. A review of the clinical history of these children revealed that 5 had previously received cobalt and iron preparations, and this appeared to be more than a chance relation. A more recent report by Roche and Layrisse[16] demonstrates a marked drop in I^{131} uptake after a week, approaching 0 after two weeks in all 12 patients given 150 mg. of cobaltous chloride per day. Subsequently, they successfully treated 2 cases of hyperthyroidism in preparation for thyroidectomy.

These clinical observations appear to leave little doubt that under certain circumstances cobalt has a goitrogenic effect. Efforts in man and animals experimentally to reproduce and elucidate the pathophysiology of cobalt goiters have been unrewarding to date. Scott and Reilly[17] could detect no change in iodine metabolism in normal or in tumor-bearing rats after cobalt administration. In another study, cobaltous chloride in daily doses of 1 to 6 mg. per kilogram of body weight in 15 children for ten weeks resulted in no clinical or laboratory evidence of thyroid dysfunction.[18] However, in 2 children receiving 6 mg. per kilogram significant depression of I^{131} uptake was noted. Therapy was discontinued until I^{131} uptake returned to normal, and after four more weeks of treatment a second depression failed to occur. Holly,[7] in giving cobalt to 78 pregnant women in doses of 60 to 100 mg. per day for at least three months, found no thyroid dysfunction in these mothers or in their newborn children. Hill et al.[19] noted no goitrogenic effect in 115 patients given daily doses of 50 to 160 mg. in adults and 10 to 50 mg. in children over periods of several months; thyroid-function studies, however, were not done. Tevetoglu[20] treated 50 children with anemia associated with poor nutrition, infection and prematurity. They ranged in age from two months to ten years, and the majority received 40 mg. of cobaltous chloride per day for periods of four to fourteen weeks. Satisfactory hematologic responses were reported, with apparently no adverse effects on thyroid function noted clinically. However, again, no thyroid-function studies were done.[20] Kirkwood and Fawcett[21] have shown that in a cell-free suspension of thyroid tissue in vitro, cobalt results in a suppression of tyrosine iodinase. As yet, there has been no substantiation of this clinically or in intact animals. What has been observed fairly constantly in the few cases reported has been a marked fall in the I^{131} uptake, followed in some cases by a rise in serum cholesterol and a fall in serum protein-bound iodine as occurs typically with other goitrogens.

Thus, though the pathophysiology remains obscure, cobalt salts appear to have a goitrogenic effect in a certain percentage of patients. Whether this is a pharmacologic response related to dosage and duration of treatment or an idiosyncratic reaction, the possible severe myxedematous state that may occur, as illustrated in this case, appears to be sufficient reason to reserve cobalt treatment for conditions other than anemias due to iron deficiency or the physiologic anemia of prematurity.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42461

PRESENTATION OF CASE

A forty-year-old man entered the hospital because of weakness.

Six months previously he noted the onset of fatigue at the end of each day. Subsequently, there were persistent weakness and easy fatigability as well as numerous upper respiratory infections that were accompanied by chills and fever. Four days before admission there was a transient episode of nausea. On the next day he vomited once after a meal. There was also a nosebleed. There were brief periods of chilliness that were followed by sweating and feverishness. On the day before entry the temperature was 104°F. On the day of admission his physician noted scleral icterus. There was no anorexia, and there was no known exposure to hepatotoxins. During the six months before entry there was a loss of 20 pounds in weight.

For twenty years the patient had worked on pig farms, where he fed the pigs and cleaned the pigpens. During the year before admission he worked in a greenhouse and as a garbage collector until two weeks before entry, when he resumed his former work in a piggery. There was a history of tuberculosis in his mother's family. He had rheumatic fever when he was sixteen years of age. He had been a lifelong resident of New England.

Physical examination revealed a well nourished, pale, icteric man. A firm node that measured 1 cm. in diameter was felt in the right axilla; a similar node that measured 0.5 cm. in diameter was noted on the left. Examination of the lungs showed occasional scattered dry rales on the right anteriorly. The heart was not enlarged; a Grade 1 apical systolic murmur was audible. Abdominal examination revealed a very firm, nontender spleen that extended to the left iliac crest. The upper border of liver dullness was at the sixth intercostal space. The edge of the liver, which was tender, was felt 3 fingerbreadths below the right costal margin.

The temperature was 102°F., the pulse 100, and the respirations 28. The blood pressure was 138 systolic, 60 diastolic.

The urine gave a +++ test for albumin, a positive benzidine test and negative tests for bile and arsenic; the sediment contained 1 red cell, 3 white cells and 3 or 4 granular casts per high-power field; culture grew out a few *Staphylococcus aureus*. The urinary urobilinogen was 16.4 Ehrlich units. Examination of the blood revealed a hemoglobin of 5.6 gm. per 100 ml., a hematocrit of 16 per cent and a white-cell count of 6100, with 51 per cent neutrophils, 24 per cent band forms, 10 per cent lymphocytes, 14 per cent monocytes and 1 per cent plasma cells. There were 2 nucleated red cells per 100 white cells. The erythrocytes showed marked polychromasia, anisocytosis and poikilocytosis. Platelets were normal in number, with some giant forms. The reticulocyte count was 18 per cent. The hemoglobin electrophoretic pattern was normal. The clotting time and clot retraction were normal. A bone-marrow aspirate was hypercellular, with abundant megakaryocytes; the myeloid-erythroid ratio was 0.5:1; a tissue section showed no granulomas; a culture was negative. The nonprotein nitrogen was 50 mg., the total protein 5.9 gm., the albumin 4.1 gm., the globulin 1.8 gm., the bilirubin 3.2 mg., the creatinine 1.1 mg., the uric acid 9.5 mg., the cholesterol 98 mg., the cholesterol esters 56 mg., and the iron 60 microgm. per 100 ml. The sodium was 128 milliequiv., the po-

FIGURE 1. *Roentgenogram of the Abdomen.*
The spleen is greatly enlarged and contains multiple irregular calcifications.

tassium 4.2 milliequiv., and the chloride 92 milliequiv. per liter. The alkaline phosphatase was 0.9 units. The prothrombin content was 67 per cent. The thymol turbidity was 2.3 units. Cephalin flocculation was negative. The serum electrophoretic pattern was normal. The Coombs test was negative, as were the Widal, heterophil-antibody and cold-agglutination tests. The brucella agglutination test was positive in a titer of 1:640. The blood Hinton test and blood cultures were negative. A throat culture grew out abundant alpha-hemolytic streptococci, moderate nonhemolytic streptococci and moderate *Neisseria catarrhalis*. Cytologic examinations of the sputum for malignant cells were doubtful, unsatisfactory and negative. The tuberculin test (O.T. 1:1000) and the coccidioidin and histoplasmin skin tests were negative. X-ray films of the chest and the abdomen, an upper gastrointestinal series, a barium-enema examination and an intravenous pyelogram were normal except for an enlarged spleen and numerous areas of amorphous calcification that appeared to be within the spleen (Fig. 1 and 2).

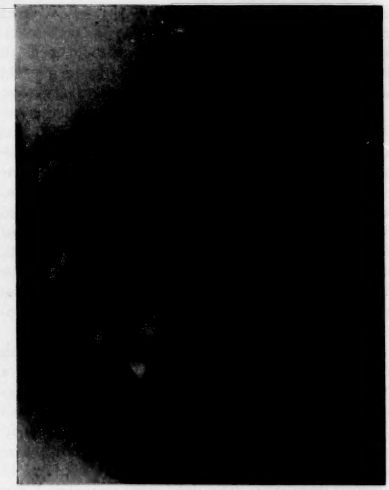

FIGURE 2. *Detailed View of the Lower Portion of the Spleen, with Two of the Calcified Nodules Included.*
The lowermost nodule shows the irregular, slender threads of calcium that reach out from the center of the lesion. The uppermost calcification has a different pattern and is partially laminated.

Meticorten therapy, 60 mg. daily, was begun on the third hospital day. By the seventh hospital day the reticulocyte count had risen to 42 per cent; the hematocrit was 37 per cent, and the temperature was normal. The serum nonprotien nitrogen was 41 mg., the uric acid 7.8 mg., and the bilirubin 1.7 mg. per 100 ml. The prothrombin content was 46 per cent. Thereafter the reticulocyte count ranged between 5 per cent and 13 per cent, the hematocrit remained at about 37 per cent, and despite Crysticillin the temperature ranged between normal and 100°F. On the sixteenth hospital day the nonprotein nitrogen was 32 mg., the uric acid 4.6 mg., the bilirubin 2.1 mg., and the iron 135 microgm. per 100 ml. The urinary urobilinogen was 0.9 Ehrlich units. A biopsy specimen of the liver showed hemosiderosis. Biopsy of a lymph node in the right axilla showed no abnormalities; a smear was negative for acid-fast bacilli, and a culture showed no growth.

On the twenty-eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JOHN B. STANBURY*: May I see the x-ray films of the chest and of the spleen?

DR. JOSEPH HANELIN: The lungs are fairly emphysematous but seem otherwise clear. There is old pleural thickening at the right base. The abdominal film shows the spleen to be large. There are multiple, large, heterogeneous calcium deposits, the largest of which is almost 3 cm. in diameter, apparently all in the spleen; they have fine tendrils that reach out peripherally — an atypical appearance (Fig. 1 and 2). The pyelogram is normal.

DR. STANBURY: In tuberculosis the calcifications are smaller than that, are they not?

DR. HANELIN: Those that we see are small and do not have tendrils.

DR. STANBURY: Do you see such deposits with infarction?

DR. HANELIN: I suppose that is conceivable. The deposition is unusual; I cannot recall a specific case of this type of calcium pattern.

DR. STANBURY: This patient had a long, febrile, debilitating course and apparently had severe hemolytic anemia. The evidence for hemolytic anemia seems good; he had a severe anemia on admission. There was acholuric jaundice, a high reticulocyte count, an elevated bilirubin, an erythroid hyperplasia of the bone marrow and a markedly elevated urinary urobilinogen. Indeed, there was a positive benzidine test on the urine.

The most arresting feature of the protocol is the occupational history. Not only was the patient closely associated with pigs for many years, but also at the time he first became ill, he worked in a greenhouse. I do not visualize any toxin with which he may have come in contact in the greenhouse that would account for the picture that he presented. Arsine is a base for many fertilizers and is used in the manufacture of certain insecticides. The arsine, itself, is not to be found in greenhouses. Of substances that are used in insecticides arsine is the only one

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that customarily may produce hemolytic anemia. I am inclined to disregard the occupation in the greenhouse.

People who are associated with pigs are also associated with rats, which are always present where pigs are, so that I must also consider diseases of rats that may have been transmitted to this man. Among these, of course, is rat-bite fever. The course was too long: moreover, I am not aware that hemolytic anemia occurs with rat-bite fever. Leptospiral infection also needs to be considered. Again, the course was too long for leptospiral infection, and there was no genuine evidence of hepatitis or the type of nephropathy that one finds with leptospiral infection. Trichinosis is another possibility, but there was nothing to suggest that. Also, one has to ingest the infected meat, rather than merely be associated with the animal vector, to acquire the disease.

There is, however, one disease of pigs that deserves serious consideration — this is, infectious abortion of pigs from *Brucella suis*. This is a fairly rare type of infectious abortion in this country. Most of the cases have been reported from the Middle West. I took the liberty of calling the Department of Health this morning to find out if any *Br. suis* had been seen in pigs in the state of Massachusetts in recent years. Yes; 8 cases had been reported in 1952, but none since. The case for brucella infection is made more arresting by the fact that the patient had a positive agglutination titer of 1:640. Shortly, I shall discuss the reliability of this test. There were features that suggested brucella infection, but I am unaware that hemolytic anemia occurs in the course of brucella infection, and I have found no report of it in a search of the literature. Furthermore, the blood and bone-marrow cultures were negative.

Are there any other diseases that may produce hemolytic anemia and a febrile course? There are a variety of them. Clostridial infections, bartonella infection in Peru, malaria — but we are told this patient was never outside New England — and infections with streptococci and staphylococci may be accompanied by profound hemolysis. There are three other infectious diseases that I want to mention in passing, because fragments of data bring them to mind. One is tuberculosis. The rales that were heard in the chest are suggestive, but there were no lesions in the films of the chest. The calcifications in the spleen suggest tuberculosis, as does the febrile course, but I am unaware that tuberculosis is ever accompanied by hemolytic anemia.

Bacterial endocarditis also comes to mind. The patient had a faint heart murmur, and at the age of sixteen had what was diagnosed as rheumatic fever, but there was little else in the record to suggest this disease. Syphilis also needs to be mentioned because in one of its forms it does give rise to hemolytic anemia and hemoglobinuria, but there is little else to support this diagnosis.

Are there any other types of hemolytic anemia that should be considered? There is cold hemolytic anemia, the march hemoglobinemia and the so-called idiopathic acquired hemolytic anemia.

Another group of diseases that deserves more serious consideration includes the so-called symptomatic hemolytic anemias. Hemolytic anemia of this degree is seen in patients with some of the collagen diseases, such as lupus erythematosus and periarteritis nodosa and, rarely, with sarcoidosis. Fairly often severe hemolytic anemia is associated with such diseases as chronic lymphatic leukemia, lymphosarcoma and Hodgkin's disease. Customarily, with chronic lymphatic leukemia and lymphosarcoma, the Coombs test is positive. It was negative in this particular case; more commonly than not, the Coombs test is negative in hemolytic anemia associated with Hodgkin's disease. There is an excellent review of the whole problem by Wasserman and his associates.[1]

Could Hodgkin's disease explain the findings? I find nothing in the protocol that is inconsistent with that diagnosis. The febrile course, the long period of fatigue, the weight loss, the anemia, the hemolytic aspect of the anemia and the large spleen are all consistent with Hodgkin's disease. I do not understand the serum iron value of 60 microgm. per 100 ml. at the time of entry. In hemolytic anemia the serum iron is at least normal and usually is elevated. I cannot account for the low serum iron in this patient unless, by chance, he had a considerable loss of hemoglobin, perhaps as hemoglobinuria before admission. I also have no way of accounting for the low value of the serum alkaline phosphatase. Another finding difficult to explain is the calcified spleen. The spleen may be calcified from a number of causes, among them tuberculosis and infarcts, which have been mentioned. Hydatid cysts of the spleen and phlebothromboses in the spleen may also become calcified. This unusual pattern of calcification means nothing specific to me.

I am left with two possible diagnoses: brucellosis and Hodgkin's disease. The diagnosis revolves to a considerable degree about the specificity of the agglutination test. The agglutination test in brucellosis is specific. Relatively few other conditions affect it. It rises in infectious mononucleosis and tends to rise in any patient with a febrile illness. A titer of 640 is nearly diagnostic. The only other way that I can explain it is by the fact that persons who work closely with infected animals may have agglutination titers that are higher than those found in the population at large. Among butchers agglutination titers may be as high as 320. I suspect that this patient, who had been in contact with pigs for a long time, had built up an immunity to *Br. suis*. The febrile disease, which I think was Hodgkin's disease, caused a nonspecific rise in the agglutination titer to 640.

The operation that was done, I assume, was a splenectomy. It is possible that it was a resection of the bone marrow for a better look or an explora-

tory laparotomy. I should like to predict that at the operation the finding was Hodgkin's disease.

DR. REED HARWOOD: How do you explain the high uric acid?

DR. STANBURY: I did not find any report of high uric acid in hemolytic anemia. I suspect that with any disease in which tissue is being destroyed the uric acid is high.

DR. HARWOOD: Is it not commonly high with leukemia?

DR. STANBURY: Yes; but I am not so sure that it is with Hodgkin's disease.

DR. ALLEN G. BRAILEY: Does not hemoglobin break down to uric acid?

DR. STANBURY: When many red cells break down, there is no significant release of uric acid.

A PHYSICIAN: In hemolytic anemia there would be a rapid turnover of nucleated red cells in the bone marrow.

DR. MORTON N. SWARTZ: Initially, we thought that brucellosis should be considered, but when we reviewed the literature, we did not find any cases of brucellosis with an associated acquired hemolytic anemia. Subsequently, numerous negative blood and urine cultures and negative histologic and bacteriologic examinations of the bone marrow and lymph nodes completely disenchanted us with this diagnosis. Preoperatively, I think the diagnosis was, as Dr. Stanbury suggested, lymphoma.

DR. WILLIAM D. SOHIER, JR.: Why could not the patient have had a brucellosis in the past that had run its course leaving an enlarged spleen and a positive agglutination? In that event the blood cultures would have been negative. The splenomegaly together with some unknown factor may then have caused hemolytic anemia, which could have accounted for the fever and the systemic symptoms; thus, one should not have to introduce another disease to account for these symptoms.

DR. SWARTZ: That was the initial thought.

CLINICAL DIAGNOSIS

Lymphoma.

DR. JOHN B. STANBURY'S DIAGNOSIS

Hodgkin's disease.

ANATOMICAL DIAGNOSES

Brucellosis of spleen, with focal calcification. (Hemolytic anemia.)

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The spleen was removed and weighed over 1200 gm. It contained dense, fibrous nodules with calcified centers that in the gross looked like tuberculomas (Fig. 3). After we saw the microscopical sections, since we were unable to find organisms microscopically and on culture that suggested anything specific, we fell back on the diagnosis of tuberculosis. The splenic tissue was very hemorrhagic, consistent with hemolytic anemia. Within the liver there was a severe degree of hemosiderosis. We were not satisfied with the diagnosis

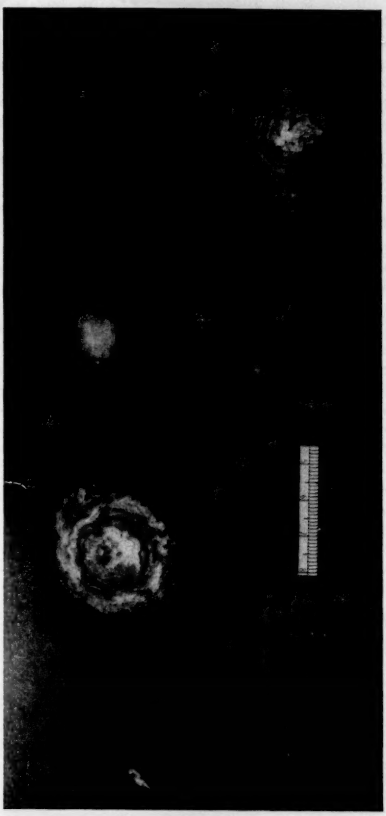

FIGURE 3.

of tuberculosis and sent some of the material to Dr. Swartz and Dr. Lawrence Kunz in the Bacteriology Laboratory for guinea-pig inoculation. Culture of the nodules in the pig grew out *Br. suis*. There was no evidence of Hodgkin's disease.

Among the literature on brucellosis there are a number of papers from the Mayo Clinic by Dr. Weed and his group,[2,3] who have emphasized to pathologists for many years the fact that all material removed at operation that is in any way suggestive of an infection, especially granulomas, should always be removed sterilely and cultured; a large

number of cases of brucellosis were in this way discovered. They have found in a few of these cases of brucella, especially in the lung, the same type of round nodules with calcifications that look exactly like a tuberculoma. Their Case 10[2] in one of the papers was of a fifteen-year-old farm boy from Minnesota who had fever, chills, weakness, anemia, increased fragility of erythrocytes and a picture compatible with hemolytic anemia. The spleen was removed; although it contained no large nodules, a culture of the splenic hilar lymph nodes and of the liver showed *Br. suis*. There were nodules in the liver. I gather that at operation in the case under discussion, the surgeon felt a large nodule in the liver also. Is that correct, Dr. Swartz?

DR. SWARTZ: Yes; there was a nodule, 2 cm. in diameter, on the inferior surface of the right lobe.

DR. CASTLEMAN: Postoperatively, I believe the patient still has hemolysis to some degree. Would you go on from there, Dr. Swartz?

DR. SWARTZ: His local physician told us that he was well. Actually, once the diagnosis was established, we wanted him to return to the hospital for treatment of the brucellosis, even though the type of lesion in the liver was circumscribed and old and would probably not have been affected by chemotherapy. The patient felt so well that he was unwilling to return for further medical care.

DR. CASTLEMAN: I thought that while he was in the hospital postoperatively he still had extensive hemolysis.

DR. SWARTZ: That has subsided.

DR. ROBERT L. BERG: Would the histologic picture be equally good for sarcoidosis or berylliosis?

DR. CASTLEMAN: No. There were none of the granulomas that are seen in sarcoidosis or berylliosis. It resembled healed granuloma, but I do not believe that this is ever seen in sarcoidosis. Calcification like that has been reported in any number of spleens, with histoplasmosis — for example, by Straub and Schwartz[4] from the Cincinnati area.

DR. HANELIN: This calcium pattern is unusual in my experience. I wonder whether the reports referred to the peculiar pattern within the nodule. These are large nodules containing dense calcium, from which fine calcium strands extend peripherally. This may prove helpful as a diagnostic clue in the future.

DR. CASTLEMAN: No such information was given.

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CASE 42462

PRESENTATION OF CASE

A fifty-six-year-old woman entered the hospital because of pain in the back.

Six weeks previously she noted a persistent, dull, occasionally sharp pain in the left side of the back, the lower ribs on this side and the left flank that radiated to the left side of the abdomen. Three weeks before admission there was abdominal tenderness in the left upper quadrant. The pain was worse when she was walking or breathing deeply. Slight constipation that required laxatives, anorexia and abdominal distention were noted. During the two weeks before entry the pain had lessened somewhat, but episodes of severe, stabbing pain every two or three days continued. During the six weeks before admission she had lost 5 pounds in weight. There was no nausea, vomiting, melena or change in color of stools.

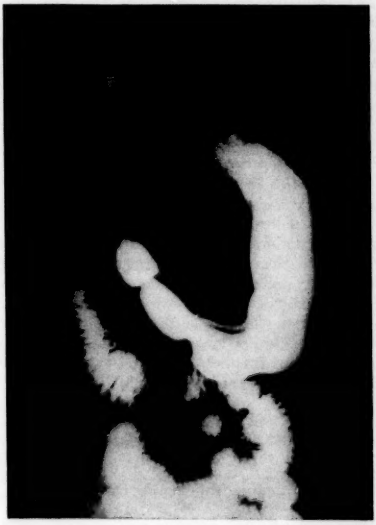

FIGURE 1. *Right Anterior Oblique View of the Stomach. The body of the stomach is displaced anteriorly.*

Ten years previously a nephrectomy on the right for renal tuberculosis was performed at another hospital. A course of streptomycin therapy was given. Subsequent intravenous pyelograms demonstrated a normal left kidney. Six months and two months before entry the patient sustained trauma to the left side of the back.

Physical examination showed a well nourished woman who was in some discomfort because of pain

in the left side of the back. Examination of the chest was negative. There was abdominal tenderness, with referred rebound tenderness and resistance in the left upper quadrant. An irregular mass was palpable just under the left costal margin lateral to the epigastrium. Peristalsis was normal. There was no abdominal distention. The peripheral pulses were normal. There was no edema.

The temperature was 98.4°F., the pulse 80, and the respirations 12. The blood pressure was 170 systolic, 90 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 12 gm. per 100 ml. and a white-cell count of 9700. The nonprotein nitrogen was 26 mg. per 100 ml., and the amylase 5 Russell units. Two stool specimens were brown and gave a negative guaiac test. Material aspirated from the stomach contained no free acid; cytologic examination for malignant cells was unsatisfactory.

X-ray films of the chest, a Graham test and a barium-enema examination were normal. An upper gastrointestinal series demonstrated anterior displacement of the body of the stomach (Fig. 1). An intravenous pyelogram showed a normally functioning left kidney that was enlarged and a small calcific density below the right transverse process of the first lumbar vertebra. Films of the thoracolumbar spine demonstrated minimal lipping along the margins of the thoracic bodies.

An operation was performed on the eleventh hospital day.

Differential Diagnosis

Dr. George L. Nardi*: This fifty-year-old woman had pain in the left flank and in the back, aggravated by deep breathing or exercise, and a palpable, tender mass in the left upper quadrant. The remainder of the data in the record are within normal limits: the laboratory findings were all negative; the x-ray findings were reportedly normal except for the enlargement of the left kidney, which I think was compensatory hypertrophy after the nephrectomy, and calcification, which may have been in a lymph node. May we look at the x-ray films?

Dr. Joseph Hanelin: I agree that no intrinsic disease is visible in the upper gastrointestinal tract. There is a suggestion of widening of the retrogastric space opposite the body of the stomach (Fig. 1). The small calcification mentioned, I am sure, is unimportant. It is not in the usual site of the mesenteric attachment of the small bowel; it could be an aftermath of the nephrectomy. The spine seems normal.

Dr. Nardi: Did the patient have any broken ribs?

Dr. Hanelin: No; I can see no broken ribs.

Dr. Nardi: Is the serration along the greater curvature of the stomach normal, or is it the finding described with blood in the leaves of the gastric serosa?

Dr. Hanelin: The irregularity along the greater curvature in this case is not excessive. Exaggeration and irregularity of the greater-curvature folds has been described with splenic rupture. I do not wish to imply that this condition was present here.

Dr. Nardi: Do you think that there might be some anterior displacement of the stomach?

Dr. Hanelin: Yes; that is correct.

Dr. Nardi: The patient had objective signs of localized peritonitis in the left upper quadrant. What could cause such a sign? It is possible that she had disease in either the splenic flexure or the stomach; however, there was no evidence — an elevated temperature and blood count or changes in the x-ray films — for either. It is possible that an adrenal tumor could produce a palpable mass that would be tender, but I think that it is unlikely here. There were no clinical signs and no other evidence of an adrenal tumor. I am left with the spleen itself. I think that the patient suffered injury to the spleen. She had a history of trauma. Although the type of trauma was not described, that is unimportant; there is no necessary relation between the severity of the trauma and rupture of the spleen. Most of these ruptures are multiple tears of the splenic capsule and require surgery to prevent exsanguination. There is another type of splenic rupture in which there is an initial phase of shock, after which the hemorrhage is arrested with sealing off by omentum or other viscera, and the patient's vital signs return to normal. There may then be a latent period, followed by recurrence of the hemorrhage. This is called delayed rupture. Most patients with hemorrhage from, or rupture of, the spleen have signs of shock, either initially or later; in addition, most of them have left-sided abdominal pain and pain referred to the shoulder through the phrenic nerve from the subdiaphragmatic irritation. This was conspicuously absent in the protocol. I should like to ask if it was absent in the record.

Dr. Rita M. Kelley: The patient did not have pain referred to the shoulder.

Dr. Nardi: Perhaps this is a reason for suspecting subcapsular rupture on admission — that is, trauma to the spleen without rupture of the capsule but with hemorrhage within the capsule and slow engorgement and enlargement of the spleen to form a palpable mass, which may or may not eventually rupture. Spontaneous rupture can occur. This type of splenic injury rarely occurs in a normal spleen. I do not think that there is any need to discuss the various metabolic, infectious and hematologic diseases of the spleen. One condition, however, I shall mention. The patient had had tuberculosis and may have had tuberculous involvement of the spleen. However, there was neither a febrile course nor clinical evidence of residual tuberculous disease. Hydatid disease might

*Assistant surgeon, Massachusetts General Hospital.

have caused the splenic enlargement. There was no eosinophilia, and I assume that she had not lived in parts of the world where she could have contracted this infestation. In both tuberculous and hydatid disease one can frequently see calcification in the spleen, and that had not been noted.

One condition that I shall seriously consider is aneurysm of the splenic artery. Such an aneurysm produces a clinical history that is similar to this patient's. Before perforation of the aneurysm there may be pain in the upper abdomen, often without radiation to the shoulder; exercise or movement may aggravate the pain, and a mass is more frequently palpated* than it is in splenic rupture or subcapsular hemorrhage. Moreover, the duration of symptoms caused by aneurysm of the splenic artery may be long — up to twelve years — whereas an intercapsular hemorrhage will rupture in a much shorter interval though it may remain intact for weeks. I should like to ask if a bruit was heard over this mass or a pulsation felt. These are the two diagnostic signs of aneurysms of the splenic artery, but they are only present in about 10 per cent of cases.

DR. KELLEY: No pulsation was felt; no bruit was heard.

DR. NARDI: Because of the history of trauma, the physical findings and the statistical frequency, I shall diagnose a contusion of the spleen, with subcapsular hemorrhage. I think that would also account for the anterior displacement of the stomach. I shall be curious to know if a splenectomy was performed and, if that was the diagnosis, why the patient remained in the hospital for eleven days before an operation was performed.

DR. HANELIN: It would be unusual from the radiographic standpoint to see a spleen of normal size that showed no obliteration of its outline, together with a well visualized renal outline and psoas shadows, and a mass produced by a splenic rupture that was large enough to displace the stomach.

DR. NARDI: Dr. Hanelin, I have the same uncomfortable sensation that I have had before, after making a diagnosis that I thought was correct and having you point out findings in an x-ray film that are completely incompatible with it. All I can say is that, on the basis of the protocol, this was the most logical diagnosis. If I had made any other, I should have simply been guessing.

DR. JOHN A. BENSON, JR.: Would you consider a lesion in the tail of the pancreas?

DR. NARDI: I think it is possible.

DR. KELLEY: The sedimentation rate was very high — 45 mm. per hour.

*Owens, J. C., and Coffey, R. J. Collective review: aneurysm of splenic artery; including report of 6 additional cases. *Internat. Abstr. Surg.* **97**:313-335, 1953.

DR. NARDI: I do not know how to interpret that; it might have been produced by the necrotic tissue, blood or neoplastic tissue.

DR. BENJAMIN CASTLEMAN: What did you think the patient had before operation, Dr. Kelley?

DR. KELLEY: We thought that she had a lesion of the tail of the pancreas.

DR. CASTLEMAN: Cancer of the tail of the pancreas?

DR. KELLEY: We thought that that was the most likely diagnosis, but we also considered lymphoma and an inflammatory process. This mass was poorly defined. She was very tender; on repeatedly examining the area we gained the impression that there was a mass. The area more medially than the usual area of splenic fullness was fuller than one would expect.

DR. WILLIAM V. MCDERMOTT, JR.: Dr. Hanelin, can you see any suggestion of a rim of calcium around the aorta?

DR. HANELIN: I do not see calcification in the wall of the aorta.

DR. CASTLEMAN: Is a carcinoma of the tail of the pancreas usually very tender?

DR. NARDI: The tenderness suggested an inflammatory process caused by infection, blood or irritation. With pancreatic obstruction I think it is statistically less frequent.

DR. BENSON: Could the calcium be in the head of the pancreas?

DR. HANELIN: It is close to it and conceivably could be within it although it lies lateral to the major portion of the head.

Dr. McDermott was asking about calcification of the abdominal aorta. There is a streak of calcium adjacent to the lumbar spine at about the third lumbar vertebra, perhaps down to and partially over the fourth lumbar vertebra; the aorta does not look unusual, other than at the plaque itself, and does not seem to be displaced away from the spine; nor is there any indication that it is displaced laterally.

DR. MCDERMOTT: Is there anything in that particular film that would lead you to think of an aneurysm of the abdominal aorta?

DR. HANELIN: Nothing that I see.

DR. JACOB LERMAN: I should like to ask Dr. Nardi if he ruled out pancreatitis on the basis of the normal amylase determination.

DR. NARDI: No; I should never do that. Although I am not sure that gallstones cause pancreatitis, they are frequently associated with it. The patient had a normal biliary tree — she never had any previous attack of abdominal pain, and she was fifty-six years of age. These facts, together with the normal amylase, the normal temperature, the findings referred to the left upper quadrant and the history of trauma, make pancreatitis an unlikely diagnosis.

Clinical Diagnosis

Carcinoma of tail of pancreas.

Dr. George L. Nardi's Diagnosis

Contusion of spleen, with subcapsular hemorrhage.

Anatomical Diagnosis

Carcinoma of tail of pancreas.

Pathological Discussion

Dr. James C. Davis: Would Dr. Wheelock like to discuss his findings?

Dr. Frank C. Wheelock, Jr.: We were suspicious preoperatively of trouble in the pancreas. It is always easier to make a diagnosis after actually seeing the patient than from reading a protocol. The problem seemed to be to differentiate pancreatitis and carcinoma. Our first choice was carcinoma. It proved to be a wildly growing carcinoma, with implants over the lesser omentum and on the greater curvature of the stomach and nearby areas. The primary mass was in the tail of the pancreas, and a biopsy of that area was taken. The patient was extremely tender, — I can vouch for that, — but I think that tenderness is not inconsistent with a rapidly growing carcinoma in any site in the abdomen.

A Physician: Why is pancreatic carcinoma frequently attended with pain? Is there an anatomical reason for it?

Dr. Wheelock: I do not know; I suppose sympathetic and parasympathetic nerves, as well as the intercostal nerves and their branches, are affected.

Dr. William H. Baker: Lymphoma in this area very infrequently causes pain.

Dr. Davis: Lymphoma does not infiltrate so much as carcinoma.

Dr. Hanelin: Some patients with retroperitoneal lymphoma have a great deal of pain.

Dr. Davis: Histologically, this carcinoma of the pancreas was an undifferentiated anaplastic one. This type is less common in the pancreas than the well differentiated adenocarcinoma. It contained isolated, completely wild cells scattered in the fibrous stroma. It had also replaced several lymph nodes.

Massachusetts Physicians Art Society

46. *No Trespassing*

Exhibited at Annual Meeting, Massachusetts Medical Society, 1956

Water Color by

Leroy D. Vandam, M.D.

Associate clinical professor of anesthesia, Harvard Medical School; director of anesthesia and surgeon, Peter Bent Brigham Hospital.

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THANKSGIVING, THAT IS

THURSDAY, November 22, according to a time-honored custom annually reaffirmed by the impressive dignity of a presidential proclamation, will be generally set apart for the observance of Thanksgiving. Although the last or the next to the last Thursday in November is traditionally so designated, every Thursday is a day of Thanksgiving in the offices of a publication whose appearance is set for this day of each week.

From the editors and their consecrated assistants thanks arise that another deadline has been met — in the case of this particular periodical approximately the six thousand seven hundred and tenth — and in the hearts of its subscribers the length (and the breadth) of the land and across the seas, gratitude that another issue of the venerable publication has been sent upon its way is presumably the prevalent emotion.

Residents of this unique area of the United States, practically redolent of thanksgiving, are additionally grateful for the opportunity afforded of spreading the cult of New England abroad.

And there are less tangible blessings for which to be thankful. The citizens of the country can be thankful that another national political campaign — approximately the fifty-third — has ended, and peace has been restored. The bitter words have been forgotten, the hatchetmen have removed their hatchets from each other's skulls and buried them elsewhere; hands have been shaken; democracy has triumphed again, even before an audience of three Soviet observers.

Oil, that unctuous liquid found so abundantly in eastern areas of the Mediterranean basin, has flowed over the troubled waters of that region, either to still them or to be ignited. The spark of a desire for freedom that seems to be so easily fanned into a burning flame is again evident in the hearts of many oppressed people, and if its contact with the oil is under temperate control there will be still more for which to be thankful.

There may even be those who can appreciate the priceless products of the relentless fashioners of the nation's private transportation system, with their sparkling new models a foot longer, a foot wider and a foot lower than ever before, designed to overlap the nation's parking meters and thrust their particolored butts out of the inadequate garages of the nation's homes. Gratitude may be expressed by the survivors that a motor fuel has been developed so much more powerful than any previous high explosive that it makes the country's dual-toned instruments of Juggernaut quicker at the getaway and faster on the road than man has ever known before, or that many a motorist will ever experience again.

PUBLIC HEALTH SERVICE COMMISSIONED RESERVE

For some time before his retirement last summer Dr. Leonard A. Scheele, the surgeon general of the United States Public Health Service, encouraged qualified physicians and other professional health personnel to apply for commissions in the Service's expanding Commissioned Reserve. This expansion is for the purpose of providing the nation with an organization prepared in advance to mobilize to meet the extraordinary public-health demands created by national emergencies related to defense. An officer in the Commissioned Reserve is given the opportunity of serving in the professional capacity for which his training and experience have fitted him, at a time when mobilization may affect every able-bodied person in the country.

Officers in the Commissioned Reserve do not receive pay while on inactive duty status. Once called to active duty, however, they will receive the pay of the grade in which commissioned, grades being equivalent to those of the Army, Navy and Air Forces — for example, from the junior assistant (equivalent to ensign in the Navy) to director (equivalent to captain in the Navy).

The program for training Commissioned Reserve officers includes a two-week course on public-health activities in national emergencies and covers such subjects as Civil Defense administration and operations; defense against radiologic, biologic and chemical warfare; and public-health aspects of natural disasters and other national emergencies. The course is given at intervals of three or four months in Washington, D. C., and eventually will be held in other locations throughout the country. In addition to this course, active-duty training with pay is available in a two-week course on epidemiology of communicable diseases and civil defense, given at the Public Health Service Communicable Disease Center in Atlanta, Georgia. The Industrial College of the Armed Forces also presents two-week conferences on national resources in 16 industrial centers throughout the country. Officers of the Commissioned Reserve stand ready to serve in locations where the emergency requires additional professional personnel to protect the health and welfare of the population and carry out public-health activities essential to survival. These would include, among others, Civil Defense control, maintenance of safe food and water supplies, waste disposal, maternal and child-health services, organization of care for the aged, the handicapped and chronically ill, psychologic support and the preparation of vital statistics. No officer will be called to active duty without his consent unless the nation is faced with an emergency requiring the mobilization of all or a substantial portion of the health resources.

Further information and application forms may be obtained from the Surgeon General, Public Health Service, Washington 25, D.C.

No one, of course, can foretell the scope or nature of a national emergency that might involve the health and lives of millions of Americans; the country can only organize in advance of such an event by pulling together persons skilled and experienced enough to meet the demands that would be placed upon everyone.

CONTROL OF WATER POLLUTION

One of the first duties of Dr. Leroy E. Burney after becoming surgeon general of the Public Health Service of the Department of Health, Education and Welfare, was to release preliminary information on the operation of the recently adopted Federal Water Pollution Control Act.

The Act, in addition to authorizing a five-year program of grants to states and to interstate water-pollution-control agencies to assist them in developing control operations, also authorizes federal grants to municipalities for assistance in the construction of sewage-treatment works as a pollution-control and water-conservation measure. Secretary Folsom, aware of the vital importance of pure and adequate supplies of water for the uses of mankind in its present modern era, has called to the attention of the governors of the states and territories the seriousness of the water-pollution problem and requested their cooperation in carrying out the state-federal provisions of the new act.

The new statute, which replaced the recently expired Water Pollution Control Act of 1948, is based on the principle that a duty of Congress is "to recognize, preserve, and protect the primary responsibilities and rights of the States in preventing and controlling water pollution." For water is, after all, an interstate and international commodity. Recurrently refined and redistilled by nature it falleth as the gentle rain from Heaven, only to be widely and grossly recontaminated by its contact with the earth's soiled surfaces.

In its practical aspects the Act authorizes grants to states and interstate agencies up to $3,000,000 a year for the next five years for water-pollution-control activities, and $50,000,000 annually, up to an aggregate of $500,000,000, for the construction of municipal sewage-treatment plants. It is comforting also to note, in view of the present attitude toward federal aid, that the Act requires the surgeon general to give consideration not only to the public benefits to be derived from a project, but the propriety of federal aid in its construction. In approving the legislation the President requested the Secretary of Health, Education and Welfare and the surgeon general to develop criteria for determining such propriety.

GENERAL PRACTITIONER OF THE YEAR

Roy Joslyn Ward, M.D., eighty-one-year-old general practitioner who for fifty-two years has given

of himself to his patients and community of Worcester, Massachusetts, has been named by his fellows in the Massachusetts Medical Society as the General Practitioner of the Year in the Commonwealth.

The honor paid not only gives just recognition for a half-century of devoted service to his profession but also points up the debt owed by this generation to such pioneers in public-health projects as Dr. Ward has been.

Early in his practice, Dr. Ward, appalled by the high death rate among infants during the summer months, urged the formation of a committee of physicians and laymen to supervise the production and distribution of clean milk at stations established throughout Worcester. Through his continued efforts the Worcester District Medical Society voted to establish a medical milk commission, for which Dr. Ward served as secretary and executive officer for many years.

Dr. Ward sponsored also the Southern Worcester County Health Association to fight tuberculosis in his community. His public-health work included service as a school physician, deputy commissioner of health and health-department epidemiologist. He helped initiate the immunization of children against diphtheria. His skill in the intubation of diphtheria patients has been long remembered.

The *Journal* takes pleasure in subscribing to the tribute now being paid to Dr. Ward by his family, patients, fellow physicians and community.

Health of Boston.—*Scarlet fever still continues with about the same mortality as heretofore. We notice 4 deaths from croup. The corresponding week of 1855 was unusually healthy, 50 deaths only having been reported, of which 6 were from consumption and 2 from croup.*

Boston M. & S. J. *November 20, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Pseudomembranous Colitis

A twenty-three-year-old gravida 3, para 2, was admitted to the hospital at thirty-eight weeks with the presumptive diagnosis of abruptio placentae.

Two previous pregnancies and the prenatal course in the current pregnancy had been normal and well supervised. A diagnosis of twins was made and confirmed by x-ray study approximately a week earlier. Despite this, weight gain had been reasonable, and there was no evidence of toxemia.

Sudden, extreme abdominal pain and collapse were reported by telephone, and the patient was sent immediately to the hospital, which was simultaneously alerted. On admission the blood pressure was 80 systolic, 60 diastolic; the hemoglobin was approximately 7 gm. per 100 ml., but there was no vaginal bleeding. She was immediately given a transfusion, and other fluids were administered intravenously while examination confirmed the diagnosis. Shortly after recovery from shock the membranes were ruptured artificially through a cervix that was found dilated 3 cm. but not effaced. A blood sample, drawn to test for afibrinogenemia, clotted promptly and did not dissolve later. After about three hours of poor labor the cervix was fully dilated, and the patient was easily delivered under nitrous oxide, oxygen and ether anesthesia of stillborn twins weighing 3 kg. (6 pounds, 8 ounces) and 2.9 kg. (6 pounds, 5 ounces). The completely separated double placenta was delivered with the second twin, and with it about 1500 to 2000 ml. of blood, mixed with numerous, very large clots. It was noted that this blood did not clot further, however, and another venous sample now failed to clot. Despite intravenous administration of oxytocics and bimanual massage of the uterus profuse hemorrhage continued from an atonic uterus. The blood pressure, which had been raised to 140 systolic, 70 diastolic, suddenly became unobtainable. Because the patient became extremely restless intravenous needles were dislodged, and it was necessary to perform a sternal puncture as well as cut-downs on both femoral veins. In all, 14 units of blood and 11 gm. of fibrinogen were given via these routes, with a resulting cessation of hemorrhage and recovery from shock. Delivery occurred at 3:15 p.m., and by 8:45 p.m. the patient was alert and rational, with a normal blood pressure. She seemed to be out of danger, but the sites of the intravenous infusions were kept open as a safety measure.

On the following day she sat up on the edge of her bed and ate small meals. It was noted with satisfaction that the urinary output was "remarkably good." By late afternoon all parenteral therapy was discontinued.

At about 10:00 p.m. she was thought by her internist to be weaker and more dyspneic than she should have been. She felt well, but seemed sicker than she looked. Because hypokalemia was suspected an electrocardiogram was taken and interpreted as confirming this diagnosis. On this basis an intravenous infusion of 1000 ml. containing 40 milliequiv. of potassium chloride was restarted. Three hours later respiratory difficulty became worse, and the pulse rose. The patient again became restless and began to cough up thin sputum. She was given elixir of terpin hydrate and codeine and 1 gm. of potassium chloride by mouth, and another dose of 20 milliequiv.

was added to the intravenous infusion. The pulse was now about 120, the respirations 40, and the blood pressure 100 systolic, 76 diastolic.

The nurse's notes report the patient as feeling better and as being coherent and rational at 7:00 a.m. Marked edema of the extremities was noted, with a pulse of 132, respirations of 44, and a blood pressure of 98 systolic, 66 diastolic.

An accurate record of fluid intake and output had not been possible during the original crisis, but one had been started at 7:00 a.m. on the day after delivery and the twenty-four-hour figures were now as follows: intake, 2600 ml. by mouth and 3425 ml. intravenously; output, 1125 ml.; totals, 6025:1125. Another electrocardiogram was taken, and further potassium chloride given by mouth. At 9 o'clock the patient refused breakfast and began to shake. Frothy sputum accompanied a profuse hyperhidrosis and was followed by coma, from which she never recovered. At 9:30 the intravenous infusions were discontinued. Half an hour later she was moribund when a final electrocardiogram was taken. Study of this and a careful review of previous tracings failed to substantiate the diagnosis of hypokalemia. She died at 12:30 p.m.

Autopsy showed a normal heart with myocardial fibers separated by edema, marked pulmonary edema and marked bilateral atelectasis secondary to a hydrothorax (800 to 900 ml. on each side). Also found was early but widespread pseudomembranous colitis.

Preventability in this case was undetermined. Skillful obstetric management of this disaster quite evidently saved the patient's life, which might easily have been lost at once. It seems fairly obvious that she died from conditions not directly related to delivery. Obviously, during the hemorrhagic episode, a careful record of intravenous totals was impossible, and it is unlikely that the amount of urine obtained during this time could have been measured. However, it is known that 11 units of whole blood — that is, at least 5500 ml. — and 11 gm. of fibrinogen were given during this disastrous period. Since 1 gm. of fibrinogen is customarily dissolved in about 200 ml., one can add at least 2200 ml. However, the patient survived this episode and was in apparently good condition by 8 p.m. Beginning at 7 o'clock the next morning and for the *following* twenty-four hours, totals recorded were 6025-ml. intake and 1125-ml. output. This, combined with the preceding day's unknown total, makes it seem entirely possible that the patient drowned. There is confirmatory physical evidence in favor of this, including a rising pulse, dyspnea, orthopnea, cough and finally the production of frothy sputum. Circulatory failure on this basis is confirmed by the autopsy findings, and, although debatable, it seems possible that the unfortunate but well intended administration of potassium accelerated this by a direct effect on the myocardium. If inclined at first to criticize this as well as the resumption of fluids intravenously, one must recall that at this time the patient appeared much sicker than she admitted. It is very gratifying, therefore, to have microscopical evidence from the autopsy to provide a plausible explanation for this — namely, pseudomembranous colitis. This condition is almost invariably fatal and usually follows abdominal surgery; in fact, its occurrence post partum in pelvic deliveries is practically unknown. It does occur, however, in cases of extreme stress and is frequently attended or preceded by the administration of large therapeutic doses of antibiotics. Certainly, this patient deserved prophylactic antibiotics, receiving in thirty-eight hours a total of 19,000,000 units of penicillin and, during the same time, 0.5 gm. of streptomycin every six hours. This caliber of medication is sufficient to alter intestinal flora, and it has been suggested that this may sometimes contribute to the occurrence of pseudomembranous colitis.

In any event it is the opinion of pathologists that this patient would have succumbed to that condition even if she had survived the serial threats of abruptio placentae, atony, hemorrhage, afibrinogenemia, circulatory failure through fluid imbalance and possibly potassium poisoning.

One might say then that this case was preventable only if the initial hemorrhage could somehow have been prevented. Obviously, this is not a reasonable expectation.

JOHN FIGGIS JEWETT, M.D.
Chairman

DEATH

LEVEK — Joseph A. Levek, M.D., of Lawrence, died on October 19. He was in his sixty-seventh year.

Dr. Levek received his degree from Tufts College Medical School in 1913. He was on the surgical staffs of the Lawrence General, Clover Hill and Bon Secours hospitals. He was a fellow of the American Medical Association and a member of the New England Pediatric Society and the Lawrence Medical Club.

He is survived by his widow, a son and daughter.

CORRESPONDENCE

RESIDENCY IN UROLOGY DESIRED

To the Editor: I am a Haitian doctor who received the degree of Doctor of Medicine from the Faculté de Médecine et de Pharmacie d'Haiti. I am serving now as third-year resident in urology at the Hôpital Général, Port-au-Prince, Haiti. I am looking for a residency-training program or a straight internship in that field in a qualified hospital of New England.

JEAN-M. VERLY, M.D.

Port-au-Prince,
Haiti (W.I.)

REGARDING PHYSICIANS PER POPULATION

To the Editor: I should like to comment on the editorial, "Physicians per Population," which appeared in the October 4 issue of the *Journal*.

It is stated that the annual requirement of new physicians to compensate for the yearly increase in population is 4362. On the other hand, according to the *Journal of the American Medical Society*, issue of May 26, 1956, 4000 physicians died during 1955. Thus, the number of physicians needed to keep the per capita ratio unchanged is 8362. During 1955, 6800 doctors graduated from American medical schools. Therefore, it appears that another 1562 physicians, or an increase of 23 per cent in the number of graduates, would have been needed to keep the ratio of 1 physician to 769 persons unchanged in the year 1955.

Another aspect of the problem is the number of physicians available to serve as house staff. According to the *Journal of the American Medical Association*, issue of September 22, 1956, there will be 7000 graduates available by July 1957, to fill 12,000 approved internships; this means that 42 per cent of the internships would remain vacant. Approximately the same percentage of residencies would remain unfilled except for the fact that the hospitals, in a desperate move, have been recruiting alien physicians abroad. In spite of their efforts, 20 per cent of all house-staff positions remain unfilled.

The figures cited above show that medical schools would have to increase the number of graduates by 23 per cent to keep up with the growth in population.

It seems to me that the medical profession itself should try to work out a solution to this problem. Otherwise the federal Government will undoubtedly take drastic measures if the doctor shortage is allowed to grow. Unless doctors correct the prevailing situation, they may well end up with socialized medicine one of these days.

JULIAN HUEBSCHER, M.D.
Los Angeles, California

Note: The intent of the editorial was not to imply that merely because the graduation of 6000 or 7000 doctors annually has satisfied the needs during the past ten years, it would continue to do so indefinitely, but rather to stress the desirability of a statistical approach to the problem. —ED.

RESCISSION OF REVOCATION OF LICENSE

To the Editor: The Board of Registration in Medicine has voted to rescind its action revoking the license of Dr. Herbert P. F. Corbin, 25 Crandall Street, Adams, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

BOOK REVIEWS

A Pictorial History of Medicine. By Otto L. Bettmann, Ph.D. With a foreword by Philip S. Hench, M.D. 4°, cloth, 318 pp., with illustrations. Springfield, Illinois: Charles C Thomas, 1956. $9.50.

Students of medical history have long anticipated this volume, for "the Bettmann Archive" in New York, founded by the author, has long been a source of medical pictures for both popular and scholarly publications. A vast and rich collection, indexed and made quickly available, had been culled for years, both in Europe and America, from books, magazines, art galleries, museums and other sources. That a pictorial history of medicine would eventuate in time was a foregone conclusion, but the amount of material to be sorted, selected and described well accounts for the years that have passed since the book was first conceived. The work has been done well, and the selection judiciously made and well produced and described. Only a few minor errors have crept in. Many of the pictures are from fundamental textbooks interspersed with those from popular literature. Both text and illustrations are, in general, excellent, and the book is a deserving tribute to both author and publisher.

HENRY R. VIETS, M.D.

Alcoholism: Its psychology and cure. By Frederick B. Rea. 12°, cloth, 143 pp. New York: Philosophical Library, 1956. $3.50.

Fifty years ago the entire problem of so-called alcoholism was an uncharted jungle; twenty-five years later pathways were started to explore it. Today, no problem is more timely or of greater interest to physicians because it is such a common condition and so many doctors have to deal with it whether they want to or not, in one form or another, directly or indirectly, as a primary or secondary factor in the patient-physician situation. Ten years ago books on the subject started to flow — first a trickle and now a widening stream.

This book is short (pocket size, indeed), matter of fact and very much to the point. It puts the cart before the horse in one sense. The first part deals with "addiction." I prefer to believe that this strong term should be applied only to the use of drugs derived from opium, but a wider usage has developed that might be described as "habituation" or "dependence." Nevertheless, the author discusses the syndrome he calls "addiction" in a reasonable and convincing manner, and the four chapters dealing with the complexity of the subject's metabolism, personality types and the onset of the condition are very informative and provocative.

The second part concerns treatment. I regret that the word "cure" is used, because medicine is so fluid and the reactions of active people can be so dynamic and unpredictable that one can truthfully only say that the "alcoholic" is "cured" so long as he remains "cured."

However, this book is well worth reading and buying because the author has a peculiar gift of communication. It is written not only for physicians but for all who are interested in this subject. It has philosophic overtones that extend beyond the four standard aversion treatments (the methods of Shadel, Voegtlin, Lemere and Thimann, including the use of apomorphine, Antabuse and medical hypnosis) into the realm that comprises the important psychologic phenomenon best described years ago by William James as conversion and participation with the work of Alcoholics Anonymous. The author manages to cover a great deal in 143 pages.

MERRILL MOORE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Doctor in Personal Injury Cases. By Harold A. Liebenson, member, Illinois, Chicago and American Bar Associations. 12°, cloth, 123 pp. Chicago: The Year Book Publishers, Incorporated, 1956. $4.00.

Infant Metabolism: Proceedings of the World Health Organization's Seminars held at Leyden and Stockholm in October-November, 1950. Edited by I. Herbert Scheinberg, associate professor of medicine, Albert Einstein College of Medicine, Yeshiva University, New York. 8°, cloth, 435 pp., with 215 illustrations and 47 tables. New York: The Macmillan Company, 1956. $8.00.

The Premarital Consultation: A manual for physicians. By Abraham Stone, M.D., associate clinical professor of preventive medicine, New York University College of Medicine, director, Margaret Sanger Research Bureau, and director, Marriage Consultation Center, Community Church,

New York City; and Lena Levine, M.D., associate medical director, Margaret Sanger Research Bureau, New York City. 8°, cloth, 90 pp., with 11 illustrations and 2 tables. New York: Grune and Stratton, 1956. $3.00.

Epilepsy and the Law: A proposal for legal reform in the light of medical progress. By Roscoe L. Barrow, dean, University of Cincinnati College of Law, and legal adviser, Special Committee on Legislation, American League Against Epilepsy; and Howard D. Fabing, M.D., chairman, Legislation Committee, American League Against Epilepsy. 8°, cloth, 177 pp. New York: Paul B. Hoeber, Incorporated, 1956. $5.50.

Die Kolposkopie in der Praxis: Einführung in die gynäkologische Krebsfrühdiagnostik. By Priv.-Doz. Dr. med. Herbert Cramer, Universitätsfrauenklinik, Frankfurt am Main. With a foreword by Prof. Dr. H. Naujoks, Frankfurt am Main. 8°, paper, 103 pp., with 121 illustrations. Stuttgart: Georg Thieme, 1956. $7.15. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Changing Concepts of Psychoanalytic Medicine: Proceedings of the Decennial Celebration of the Columbia University Psychoanalytic Clinic, March 19 and 20, 1955. Edited by Sandor Rado, M.D., D.Pol.Sc., clinical professor of psychiatry, and director, Psychoanalytic Clinic for Training and Research, Columbia University College of Physicians and Surgeons; and George E. Daniels, M.D., clinical professor of psychiatry, and associate director, Psychoanalytic Clinic for Training and Research, Columbia University College of Physicians and Surgeons. 8°, cloth, 248 pp., with illustrations and tables. New York: Grune and Stratton, 1956. $6.75.

Textbook of Urology. By Victor F. Marshall, M.D., associate professor of clinical surgery (urology), Cornell University Medical College, attending surgeon-in-charge, urology, James Buchanan Brady Foundation of the New York Hospital, and associate attending urologist, Memorial Center for Cancer and Allied Diseases, New York City. 8°, cloth, 268 pp., with 66 illustrations. New York: Paul B. Hoeber, Incorporated, 1956. $5.50.

Bibliographie der Sportmedizin und ihrer Grenzgebiete 1955. Edited by a commission of the German Sports Physicians Confederation by Dr. med. E. J. Klaus, lecturer, sports medicine, Univ. Münster/W., and chairman, Sports Physician Confederation, Westfalen. 8°, paper, 96 pp. Stuttgart: Georg Thieme, 1956. DM 3.60. $0.85. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

Great Men: Psychoanalytic studies. By Edward Hitschmann, M.D. With a foreword by Ernest Jones. 8°, cloth, 278 pp. New York: International Universities Press, Incorporated, 1956. $4.00.

Die Septische Thrombophlebitis: Ihre Entstehung und Ausbreitung auf dem Blutwege: Was leistet die Venenunterbindung? By Dr. Fritz Felsenreich, Vienna; and Dr. A. Kristinsky, Vienna. 8°, paper, 94 pp., with 20 illustrations and 5 tables. Vienna: Wilhelm Maudrich, 1955. $2.88. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

NONCLINICAL NOTES

BOSTON SURGICAL SOCIETY

On November 5, 1956, at a dinner at the Harvard Club of Boston, Dr. Arthur W. Allen, president of the Boston Medical Library and former president of the Massachusetts Medical Society and the American College of Surgeons, was presented with the Henry Jacob Bigelow Medal of the Society. After the presentation Dr. Allen addressed the Society on "The Development of Surgery for Lesions of the Stomach and Duodenum."

The Bigelow Medal has been awarded on only 13 previous occasions, the latest recipient having been Dr. Edward D. Churchill, in 1955.

NOTICES

ANNOUNCEMENTS

Dr. Warwick Potter announces the opening of an office at Argilla and Heartbreak Road, Ipswich, Massachusetts, for the practice of pediatrics.

Dr. Benjamin F. Gill announces the removal of his office to 270 Commonwealth Avenue, Boston, for the practice of psychiatry.

BENJAMIN WATERHOUSE MEDICAL HISTORY SOCIETY

A dinner meeting of the Benjamin Waterhouse Medical History Society of Boston University School of Medicine will be held at the Massachusetts Memorial Hospitals, Boston, on Monday, November 26, at 6 p.m.

Dr. Benjamin Spector will give a talk entitled "A Précis of Surgical Thought and Practice in Ancient Greece and Rome." All interested persons are invited.

JEWISH MEMORIAL HOSPITAL

A medical-staff meeting will be held at the Jewish Memorial Hospital, Roxbury, on Wednesday, November 21, at 8 p.m.

Dr. Sidney Farber will give a talk entitled "Progress in Cancer Research."

ROBERT S. JOHNSON, JR., MEMORIAL LECTURE

The first annual lecture of the Robert S. Johnson, Jr., Memorial Lectures will be held at the Boston State Hospital, Monday, November 19, at 8:30 p.m.

The lecture will be presented by Dr. Francis J. Braceland, president, American Psychiatric Association, psychiatrist-in-chief, Institute of Living, who will speak on the subject "Schizophrenia and Historical Perspectives."

AMERICAN COLLEGE OF CHEST PHYSICIANS AND OVERHOLT THORACIC CLINIC

There will be a combined meeting of the New England States Chapter of the American College of Chest Physicians and the Overholt Thoracic Clinic in the Joslin Auditorium of the New England Deaconess Hospital, Boston, on Wednesday, November 21, at 4 p.m.

Dr. Maurice Sones will give a talk entitled "Course of Sarcoidosis."

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 16. American Public Health Association. Page 675, issue of October 4.
NOVEMBER 16–22. Pan-Pacific Surgical Association. Page 490, issue of September 6.
NOVEMBER 16–29. Consultation Clinics for Crippled Children in Massachusetts. Page 828, issue of October 25.
NOVEMBER 18–22. Pan American Medical Association. Page 490, issue of September 6.
NOVEMBER 19. Robert S. Johnson, Jr., Memorial Lecture. Page 971.
NOVEMBER 20. South End Medical Club. Page 923, issue of November 8.
NOVEMBER 20. Harvard Medical Society. Page 923, issue of November 8.
NOVEMBER 20, 27, 29 and DECEMBER 4 and 18. Boston City Hospital House Officers' Association. Page 875, issue of November 1.
NOVEMBER 21. Jewish Memorial Hospital. Page 971.
NOVEMBER 21. American College of Chest Physicians and Overholt Thoracic Clinic. Page 971.
NOVEMBER 26. Benjamin Waterhouse Medical History Society. Page 971.
NOVEMBER 28. Phi Delta Epsilon. Page 831, issue of October 25.
NOVEMBER 28. Middlesex County Sanatorium. Page 831, issue of October 25.
NOVEMBER 28 and DECEMBER 12. Walter E. Fernald State School. Page 728, issue of October 11.
NOVEMBER 28–30. American College of Cardiology. Page 731, issue of October 11.
DECEMBER 1–15. Bahamas Medical Conference. Page 923, issue of November 8.
DECEMBER 2. American Academy of Dental Medicine. Page 923, issue of November 8.
DECEMBER 7 and 8. Association for Research in Nervous and Mental Disease. Page 923, issue of November 8.
DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
JANUARY 17, 1957. Arthritis Study Unit. Page 831, issue of October 25.
APRIL 27, 1957. Postgraduate Medical Institute. Page 785, issue of October 18.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 22

THURSDAY, NOVEMBER 22
Holiday

FRIDAY, NOVEMBER 23
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Sulfonylurea Compounds. Dr. Raffael Camerini. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham presiding. Auditorium, Carney Hospital, Dorchester.
*12:30–1:30 p.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, NOVEMBER 24
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Anesthesiology Conference. Dr. Benjamin Etsten. Anesthesia Laboratory, New England Center Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Hematology Conference. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, NOVEMBER 26
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Tumor Conference. Dr. C. C. Lund and members of the Tumor Board. Dowling Amphitheater, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Endocrine Conference. Dr. Astwood. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–5:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Dr. Benjamin Etsten, Stearns Auditorium, New England Center Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. Edward T. MacMahon. Stearns Auditorium, New England Center Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference of Greater Boston. (A) Importance of Preoperative Rounds. (B) Importance of Postoperative Rounds. Dr. Benjamin Etsten. Auditorium, Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

TUESDAY, NOVEMBER 27
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, NOVEMBER 28
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry Conference. Drs. John F. Sullivan, Justin Hope and Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Symposium on Pulmonary Disease. Middlesex County Sanatorium, 775 Trapelo Road, Waltham.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*4:00–6:00 p.m. Postgraduate Seminar in Pediatric Neuropsychiatry. Research Laboratories, Walter E. Fernald State School, Trapelo Road, Waltham.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*6:30 p.m. Lahey Clinic Lecture. Panel discussion. Gastric Ulcer and Malignancy. Dr. Samuel F. Marshall, moderator. Drs. Everett D. Kiefer, William R. Meissner and Robert E. Wise. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.